# CSP #425

# Naltrexone in the Treatment of Alcoholism

The VA Naltrexone Cooperative Study was designed to determine whether using the drug naltrexone would help reduce drinking in alcohol-dependent patients. In this study, 627 veterans were randomized to placebo or one of two naltrexone treatments. All patients received anti-drinking counseling. Data on alcohol intake and compliance to medication were measured for one year. There were no differences in alcohol use between the placebo and naltrexone groups.

It was decided to use the data collected in this study to see what methods were useful in helping patients to remember to take their medication and whether any of these methods led to reduced drinking. The data showed that the patients who took their study medication, either naltrexone or placebo, regularly drank less than those patients who did not. The data also showed there are strategies which can help patients take their medication more regularly.

## Medication Compliance Feedback and Monitoring in a Clinical Trial: Predictors and Outcomes

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**Abstract:** *Objective:* The objective of this study was to demonstrate the utility of continuous monitoring and enhancement of medication compliance during a long-term clinical trial, predictors of compliance and relationships to drinking outcomes.

*Methods*: Alcohol-dependent patients enrolled in a multicenter VA cooperative study were randomly assigned to once-daily naltrexone (NTX) for 3 or 12 months (short-term or long-term NTX) or placebo for 12 months of treatment. All medications were dispensed in bottles with medication event monitoring (MEMS, AARDEX, Union City, CA) caps with a microprocessor that recorded openings as presumptive doses. Patients were trained to develop personal cues as dosing reminders. Monthly feedback sessions included review of compliance data and cues.

*Results*: There were no significant differences among short-term NTX, long-term NTX, and placebo (209 each) groups in measures of compliance. Overall compliance rates were 71% $\pm$ 31% of doses for the first 13 weeks and 43% $\pm$ 33% of doses over 52 weeks. Some doses were taken during 83% $\pm$ 27% of the first 13 weeks. Higher medication compliance predicted fewer drinks per drinking day (P=.02) throughout follow-up and a lower percentage of drinking days (P=.002 during the first 13 weeks) with no significant effect for treatment group.

*Conclusions:* The feedback and monitoring programs were important

features to demonstrate that lack of treatment effect was not a result of poor compliance. Medication compliance data supported the internal validity of the trial by demonstrating that good compliers had better outcomes, irrespective of treatment with NTX or placebo. The MEMS feedback methodology is feasible for use in multicenter trials.

*(Value in Health 6(5):566-573, 2003)*
*CSPCC Perry Point, MD*

# CSP #97-010

# Veteran Women's Alcohol Problems

This paper on screening for hazardous drinking and alcohol use disorders in women veterans was conducted as part of a larger VA funded study of Veteran Women's Alcohol Problems. In this study, women veterans who used the Women's Clinic at the VA Puget Sound Health Care System were invited to complete one or more mail surveys that asked questions about their past health, current health status, and health practices. The survey was mailed in 1998, 1999, and 2000. Detailed in-person interviews about PTSD and drinking behaviors were conducted on a subset of women who completed the surveys. This study has resulted in numerous papers about PTSD, drinking, and other aspects of women's health.

Primary care physicians need a brief alcohol questionnaire that identifies hazardous drinking and alcohol use disorders in women. Two tests have been validated in male VA patients, but not in women. Three hundred ninety three female VA patients completed the 10-item Alcohol Use Disorders Identification Tests (AUDIT), and a previously proposed change to the AUDIT question 3 with a sex specific threshold for binge drinking. A modification of the AUDIT, the AUDIT-C (the first 3 questions of the AUDIT) was also used. Responses to these 3 scales (10 item AUDIT, question 3 AUDIT, and AUDIT-C) were compared with past hazardous drinking or active alcohol abuse or dependence as reported in the interviews. In this study, 23% of women veterans met criteria for hazardous drinking or alcohol abuse or dependence. The results of this study indicate that the AUDIT-C and the sex specific AUDIT-C are effective screening tools for identifying female veterans with hazardous drinking or alcohol abuse or dependence.

## Two Brief Alcohol-Screening Tests from the Alcohol Use Disorders Identification Test (AUDIT)

BRADLEY KA, BUSH KR, EPLER AJ, DOBIE DJ, DAVIS TM, SPORLEDER JL, MAYNARD C, BURMAN ML, KIVLAHAN DR

**Abstract:** *Background*: Primary care physicians need a brief alcohol questionnaire that identifies hazardous drinking and alcohol use disorders. The Alcohol Use Disorders Identification Test (AUDIT) questions 1 through 3 (AUDIT-C), and AUDIT question 3 alone are effective alcohol-screening tests in male Veterans Affairs (VA) patients, but have not been validated in women.

*Methods*: Female VA patients (n = 393) completed self-administered questionnaires, including the 10-item AUDIT and a previously proposed modification to AUDIT question 3 with a sex-specific threshold for binge drinking (>/=4 drinks/occasion), and in-person interviews with the Alcohol Use Disorder and Associated Disabilities Interview Schedule. The AUDIT-C, AUDIT

question 3 alone, and the 10-item AUDIT were each evaluated with and without the sex-specific binge question and compared with past-year hazardous drinking (>7 drinks/week or >/=4 drinks/occasion) and/or active Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition alcohol abuse or dependence, based on interviews.

*Results:* Eighty-nine women (22.6%) met interview criteria for past-year hazardous drinking and/or active alcohol abuse or dependence. Standard and sex-specific AUDIT-Cs were sensitive (0.81 and 0.84, respectively) and specific (0.86 and 0.85, respectively). Their areas under the receiver operating characteristic curves were equivalent (0.91, and 0.92, respectively) and slightly higher than for the standard 10-item AUDIT (0.87). A single, sex-specific question about binge drinking (modified AUDIT question 3) had a sensitivity of 0.69 and specificity of 0.94, whereas the standard AUDIT question 3 was specific (0.96) but relatively insensitive (0.45).

*Conclusions:* The standard and sex-specific AUDIT-Cs are effective screening tests for past-year hazardous drinking and/or active alcohol abuse or dependence in female patients in a VA study.

*(Arch Intern Med 163:821-829, 2003)*
*ERIC Seattle, WA*

# CSP #379

# Aneurysm Detection and Management (ADAM)

The Aneurysm Detection and Management (ADAM) Study was carried out in 16 Veterans Affairs medical centers during the period of 1992-2000. The study randomized 1136 patients at good surgical risk, aged 50 to 79 years, with abdominal aortic aneurysms (AAA) 4.0 to 5.4 cm in diameter to either immediate open surgical AAA repair or to imaging surveillance every 6 months with repair reserved for AAAs that became symptomatic or enlarged to 5.5 cm. Overall, there was no significant difference in all-cause mortality (primary outcome) or AAA-related mortality (secondary outcome) between immediate open surgical repair and imaging surveillance.

Health-related quality-of-life measurements were collected during long-term follow-up (3.5 to 8 years), including the SF-36 health status questionnaires, prevalence of impotence, and maximum activity level. For most quality-of-life measures there was no difference between randomized groups. However, immediate repair resulted in a higher prevalence of impotence one year after repair but was also associated with improved perception of general health in the first 2 years after repair compared to imaging surveillance.

## Quality Of Life, Impotence, And Activity Level In A Randomized Trial Of Immediate Repair Versus Surveillance Of Small Abdominal Aortic Aneurysm

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**Abstract:** O*bjective*: We compared long-term health-related quality-of-life outcome after randomization to immediate elective repair or imaging surveillance, and in relation to time of elective repair, in patients with small asymptomatic abdominal aortic aneurysm (AAA).

*Methods:* This randomized clinical trial was carried out in 16 Veterans Affairs medical centers. Study subjects were patients at good surgical risk, aged 50 to 79 years, with AAAs 4.0 to 5.4 cm in diameter. Interventions included immediate open surgical AAA repair or imaging surveillance every 6 months with repair reserved for AAAs that became symptomatic or enlarged to 5.5 cm. Main outcome measures considered were SF-36 health status questionnaire, prevalence of impotence, and maximum activity level, which were determined at randomization and at all follow-up visits.

*Results:* Eleven hundred thirty-six patients were randomized and followed up for 3.5 to 8 years (mean, 4.9 years). The two randomized groups did not differ significantly for most SF-36 scales at most times, but the

immediate repair group scored higher overall in general health (P <.0001), which was particularly evident in the first 2 years after randomization, and slightly lower in vitality (P <.05). The baseline value of one SF-36 scale, physical functioning, was an independent predictor of mortality. Overall, more patients became impotent after randomization to immediate repair compared with surveillance (P <.03), but this difference did not become apparent until more than 1 year after randomization. Maximum activity level did not differ significantly between the two randomized groups, but decline over time was significantly greater in the immediate repair group (P <.02).

*Conclusions:* For most quality-of-life measures and times there was no difference between randomized groups. Immediate repair resulted in a higher prevalence of impotence more than 1 year after randomization, but was also associated with improved perception of general health in the first 2 years.

*(J Vasc Surg 38 (4):745-52, 2003)*
*CSPCC West Haven, CT*

# CSP #027

## 18-F-Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) Imaging in Patients with Solitary Pulmonary Nodules: Economic Study

Lung cancer is the most common cause of cancer death in both men and women in the United States. Once a diagnosis of lung cancer is made, staging tests are performed to determine if lung cancer has spread to other parts of the body, including lymph nodes located in a compartment of the chest known as the mediastinum. In general, patients with lung cancer potentially can be cured by surgery, but only if the tumor has not spread to the mediastinal lymph nodes or other distant organs. In this study, we evaluated the diagnostic accuracy of two imaging tests for lung cancer staging: computed tomography (CT) and positron emission tomography (PET). CT (or CAT) scans are routinely used for lung cancer staging in current clinical practice, but they provide limited information because they characterize lymph nodes on the basis of size, which is an imperfect surrogate for tumor involvement. PET is a relatively new but expensive test that identifies cancer cells based on their rapid metabolic rates instead of their anatomic characteristics. The solitary pulmonary nodule, otherwise known as a "spot on the lung" is a small, spherical shadow seen on a chest x-ray that sometimes represents lung cancer. We are reporting the results of three economic studies.

In the first publication, we systematically reviewed all published reports of PET and CT scanning for mediastinal staging in patients with the most common type of lung cancer and used statistical methods to synthesize the results of the studies. We found that PET was considerably more accurate than CT, and that the accuracy of PET depended on whether or not the CT scan showed enlarged mediastinal lymph nodes. Both true positive and false positive test results were more common in patients with enlarged lymph nodes on CT. Thus, while PET appears to be more accurate than CT for mediastinal staging, the relatively large number of false positive test results suggests that positive findings on PET scan still require confirmation by biopsy before a patient can be excluded from potentially curative surgery.

In the second study, we evaluated the cost-effectiveness of PET imaging and other tests for management of individuals with lung nodules. An analysis of published studies was used to estimate the accuracy of PET scans. The effect of untreated cancer was estimated from a study of Medicare patients. The scientific literature was examined to estimate the accuracy and complications of other

diagnostic tests, including computerized tomography (CAT scan), needle biopsy, and surgery. This information was combined with cost data into a model of 40 different possible ways of managing patients with solitary nodules. It was determined that the use of PET imaging is most cost-effective when patient and nodule characteristics indicate that the probability of lung cancer is low (<40%), and CAT scan findings do not suggest a benign diagnosis.

Because PET uses a short-lived radioactive chemical and expensive equipment and staff, it is a high-cost technology. In the third paper, we surveyed managers of eight PET centers to estimate the cost of synthesizing the chemical and conducting scans. Total mean cost per scan when the radioactive chemical is manufactured on-site is $1885. Centers that purchased the chemical had similar costs. Because both PET and cyclotron facilities have high fixed costs, increasing the number of scans performed and number of doses made may lead to a decrease in unit costs.

## Test Performance of Positron Emission Tomography and Computed Tomography for Mediastinal Staging in Patients with Non–Small-Cell Lung Cancer: A Meta-Analysis

MK GOULD, WG KUSCHNER, CE RYDZAK, CC MACLEAN, AN DEMAS, H SHIGEMITSU, JK CHAN, DK OWENS

**Abstract:** *Purpose:* To compare the diagnostic accuracy of computed tomography (CT) and positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG) for mediastinal staging in patients with non–small-cell lung cancer and to determine whether test results are conditionally dependent (the sensitivity and specificity of FDG-PET depend on the presence or absence of enlarged mediastinal lymph nodes on CT).

*Data Sources:* Computerized search of MEDLINE, EMBASE, BIOSIS, and CancerLit through March 2003 and reference lists of retrieved studies and review articles.

*Study Selection:* Studies in any language that examined FDG-PET for mediastinal staging in patients with known or suspected non–small-cell lung cancer, enrolled at least 10 participants (including at least 5 participants with mediastinal metastasis), and provided enough data to permit calculation of sensitivity and specificity for identifying lymph node involvement.

*Data Extraction:* One reviewer (of non-English-language studies) or 2 reviewers (of English-language studies) independently evaluated studies for inclusion, rated methodologic quality, and abstracted relevant data.

*Data Synthesis:* Thirty-nine studies met inclusion criteria. Methodologic quality varied, but few aspects of study quality affected diagnostic accuracy. The authors constructed summary receiver-operating characteristic curves for CT and FDG-PET. Positron emission tomography with 18-fluorodeoxyglucose was more accurate than CT for identifying lymph node involvement ($P$ < 0.001). For CT, median sensitivity and specificity were 61% (interquartile range, 50% to 71%) and 79% (interquartile range, 66% to 89%), respectively. For FDG-PET, median sensitivity and specificity were 85% (interquartile range, 67% to 91%) and 90% (interquartile range, 82% to 96%), respectively. Fourteen studies provided information about the conditional test performance of CT and FDG-PET. Positron emission tomography with 18-fluorodeoxyglucose was more sensitive but less specific when CT showed enlarged lymph nodes (median sensitivity, 100% [interquartile range, 90% to 100%]; median specificity, 78% [interquartile range, 68% to 100%]) than when CT showed no lymph node enlargement (median sensitivity, 82% [interquartile range, 65% to 100%]; median specificity, 93% [interquartile range, 92% to 100%]; $P$ = 0.002)

*Conclusions:* Positron emission tomography with 18-fluorodeoxyglucose is more accurate than CT for mediastinal staging. Positron emission tomography with 18-fluorodeoxyglucose is more sensitive but less specific when CT shows enlarged mediastinal lymph nodes.

*(Annals of Internal Medicine 139(11):879-892, 2003)*
*CSPCC Palo Alto, CA*

# Cost-effectiveness of Alternative Management Strategies for Patients with Solitary Pulmonary Nodules

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**Abstract:** *Background:* Positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG) is a potentially useful but expensive test for diagnosis of solitary pulmonary nodules. We evaluated the cost-effectiveness of strategies for pulmonary nodule diagnosis. We specifically aimed to compare strategies that did and did not include FDG-PET.

*Method:* Accuracy and complications of diagnostic tests were estimated by using meta-analysis and literature review. Modeled survival was based on data from a large tumor registry. Cost estimates were derived from Medicare reimbursement and other sources. Forty clinically plausible combinations of five diagnostic interventions, including computed tomography (CT), FDG-PET, transthoracic needle biopsy, surgery and watchful waiting.

*Results:* The cost-effectiveness of strategies depended critically on the pre-test probability of malignancy. For patients with low pre-test probability (26%), strategies that employed FDG-PET selectively when CT results were possibly malignant cost as little as $20,000 per QALY gained. For patients with high pre-test probability (79%), strategies that employed FDG-PET selectively when CT results were benign cost as little as $16,000 per QALY gained. For patients with intermediate pre-test probability (55%), FDG-PET strategies cost over $220,000 per QALY gained, because they were more costly but only marginally more effective than CT-based strategies.

The choice of strategy also depended on the risk of surgical complications, the probability of non-diagnostic needle biopsy, the sensitivity of CT and patient preferences regarding time spent in watchful waiting. In probabilistic sensitivity analysis, FDG-PET strategies were cost saving or cost less than $100,000 per QALY gained in 76.7%, 24.4% and 99.9% of computer simulations for patients with low, intermediate and high pre-test probability, respectively.

*Conclusions:* FDG-PET should be employed selectively when pre-test probability and CT findings disagree, or in patients with intermediate pre-test probability who are at high risk for surgical complications. In most other circumstances, CT-based strategies result in similar QALYs and lower costs.

*(Annals of Internal Medicine 138(9):724-735, 2003)*
*CSPCC Palo Alto, CA*

# The Cost of Positron Emission Tomography

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**Abstract:** *Objective:* Positron emission tomography (PET) is a high-cost imaging tool primarily used in oncology, cardiology and neuropsychiatry. Accurate estimates of the cost of PET are needed to assess its cost-effectiveness and appropriate role in clinical applications. We performed a survey- based cost analysis of PET imaging with F-18 fluorodeoxyglucose (FDG) by estimating direct, indirect, and capital costs from eight PET centers. A breakdown of the operational budget of PET centers and FDG compounding facilities is presented along with per scan costs. Differences in costs between sites that purchase and manufacture FDG are also examined.

*Materials and Methods:* We sent surveys to managers of eight Veterans Affairs (VA) and two non-VA PET scanning and FDG compounding facilities. The survey included questions about service volume and the direct costs of equipment, personnel, space, supplies, and repairs used in FDG compounding and PET imaging and interpretation. We estimated indirect costs associated with FDG compounding, PET imaging, and PET interpretation.

*Results.* Of the eight sites that responded, three sites manufactured FDG on site, three sites purchased FDG, and two sites did both. Total mean cost per scan when FDG is manufactured is $1885 and when purchased it is $1898.

*Conclusion.* PET imaging is expensive. The cost is similar when FDG is manufactured or purchased. Because both PET and cyclotron facilities have high fixed costs, increasing the number of scans performed and number of doses made may lead to a decrease in unit costs.

*(American Journal of Roentgenology 181(2):359-65, 2003)*
*CSPCC Palo Alto, CA*

# CSP #380

# Prospective Evaluation of Risk Factors for Large (>1 cm) Colonic Adenomas in Asymptomatic Subjects

As part of a comprehensive study of risk factors for advanced colon neoplasia, self reported family history, defined as first degree relatives with colon cancer, was recorded for all patients. All patients underwent complete colonoscopy and were classified by the most advanced histologic finding. With these data it was possible to evaluate the increase in risk among parents and siblings associated with advanced neoplasia. As reported below, the presence of an advanced neoplastic lesion in study patients was significantly related to higher risk of colorectal cancer in first degree relatives. The importance of this finding is that patient counseling following colonoscopy should include counseling about increased risk among first degree relatives for those patients with advanced neoplastic lesions.

## First-Degree Relatives of Patients with Advanced Colorectal Adenomas Have an Increased Prevalence of Colorectal Cancer

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DAVID A. LIEBERMAN, AND THE VETERANS AFFAIRS COOPERATIVE STUDY GROUP #380

**Abstract**: *Background & Aims*: The risk of colorectal cancer in relatives of patients with adenomatous colonic polyps is not well defined. This study assessed whether finding colonic neoplasia during screening colonoscopy was related to the family history of colorectal cancer among the participants' parents and siblings.

*Methods*: Self-reported family history of colorectal cancer was recorded for all participants in a screening colonoscopy study. The size and location of all polyps were recorded before their removal and histologic examination. Participants were grouped according to the most advanced lesion detected.

*Results*: Three thousand one hundred twenty-one patients underwent complete colonoscopic examination. Subjects with adenomas were more likely to have a family history of colorectal cancer than were subjects without polyps (odds ratio [OR], 1.36; 95% confidence interval [CI], 1.09 – 1.70). The finding of a small (<1 cm) tubular adenoma as the most advanced lesion was associated with only a modest increase in the OR of colorectal cancer in family members (OR, 1.26; 95% CI, 0.99 – 1.61), but the presence of an advanced adenoma was associated with a higher OR (OR 1.62; 95% CI, 1.16 – 2.26). Younger age of adenoma diagnosis was not related to a higher prevalence of a family history of colorectal cancer.

*Conclusions*: Relatives of patients with advanced colorectal adenomas have an increased risk of colorectal cancer. Individuals with advanced colorectal adenomas should be counseled about the increased risk of colorectal cancer among their relatives.

*(Clin Gastroenterology and Hepatology 1:96-102, 2003)*
*CSPCC Perry Point, MD*

There is evidence that screening programs for colorectal cancer can reduce mortality. Complete colonoscopy is the optimal screening procedure, but its feasibility for general screening is constrained by limited resources. This has led to focus screening on high-risk subgroups of patients. Toward this goal, numerous studies have identified potential risk factors for defining these subgroups. The study reported below was designed to incorporate features missing from previous studies: a study population large enough to provide high power to evaluate previously identified potential risk factors in combination; all patients underwent complete colonoscopy such that a large polyp free control group was available for comparison. Risk factors such as family history and smoking were confirmed to be highly associated with advanced colon neoplasia. The use of non-steroidal anti-inflammatory drugs (NSAIDS) and vitamin D intake were associated with lower levels of risk.

## Risk Factors for Advanced Colonic Neoplasia and Hyperplastic Polyps in Asymptomatic Individuals

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**Abstract:** *Context*: Knowledge of risk factors for colorectal neoplasia could inform risk reduction strategies for asymptomatic individuals. Few studies have evaluated risk factors for advanced colorectal neoplasia in asymptomatic individuals, compared risk factors between persons with and without polyps, or included most purported risk factors in a multivariate analysis.

*Objective*: To determine risk factors associated with advanced colorectal neoplasia in a cohort of asymptomatic persons with complete colonoscopy.

*Design, Setting, and Partici-pants*: Prospective, cross-sectional study of 3121 asymptomatic patients aged 50 to 75 years from 13 Veterans Affairs medical centers conducted between February 1994 and January 1997. All participants had complete colonoscopy to determine the prevalence of advanced neoplasia, defined as an adenoma that was 10 mm or more in diameter, a villous adenoma, an adenoma with high-grade dysplasia, or invasive cancer. Variables examined included history of first-degree relative with colorectal cancer, prior chole-cystectomy, serum cholesterol level, physical activity, smoking, alcohol use, and dietary factors.

*Main Outcome Measures*: An age-adjusted analysis was performed for each variable to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) associated with having advanced neoplasia compared with having no polyps. We developed a multivariate logistic regression model to identify the most informative risk

factors. A secondary analysis examined risk factors for having hyperplastic polyps compared with having no polyps and compared with having advanced neoplasia.

*Results*: The hundred twenty-nine participants had advanced neoplasia and 1441 had no polyps. In multivariate analyses, we found positive associations for history of a first-degree relative with colorectal cancer (OR, 1.66; 95% CI, 1.16-2.35), current smoking (OR, 1.85; 95% CI, 1.33-2.58), and current moderate to heavy alcohol use (OR, 1.02; 95% CI, 1.01-1.03). Inverse associations were found for cereal fiber intake (OR, 0.95; 95% CI, 0.91-0.99), vitamin D intake (OR, 0.94; 95% CI, 0.90-0.99), and use of nonsteroidal anti-inflammatory drugs (NSAIDs) (OR, 0.66; 95% CI, 0.48-0.91). In the univariate analysis, the inverse association was found with cereal fiber intake greater than 4.2 g/d, vitamin D intake greater than 645 IU/d, and daily use of NSAIDs. Marginal factors included physical activity, daily multivitamin use, and intake of calcium and fat derived from red meat. No association was found for body mass index, prior cholecystectomy, or serum cholesterol level. Three hundred ninety-one patients had hyperplastic polyps as the worst lesion found at colonoscopy. Risk variables were similar to those for patients with no polyps, except that past and current smoking were associated with an increased risk of hyperplastic polyps.

*Conclusions*: Our data endorse several important risk factors for advanced colonic neoplasia and provide a rationale for prudent risk reduction strategies. Further study is needed to determine if lifestyle changes can moderate the risk of colorectal cancer.

*(JAMA 290:2959-2967, 2003)*
*CSPCC Perry Point, MD*

# CSP #709D

# Study of Prostate Cancer in Black and White U.S. Veterans

Prostate cancer is diagnosed in approximately 334,500 men each year and accounts for nearly 41,800 deaths in the United States. Prostate cancer is the leading cancer affecting veterans and the second leading cancer among all Americans. The causes of prostate cancer and, particularly, the reasons for the unusually high incidence rates in African-Americans remain obscure. Despite strong circumstantial evidence, neither epidemiologic studies nor basic sciences have produced clear insight into the etiologic role of hormones. However, recent observations regarding androgen receptor gene polymorphisms and their relation to endocrine expression and prostate cancer risk may be providing important clues as to how an etiologic role might be mediated at the molecular level.

The article described below presents preliminary results from the study regarding racial variation in CAG repeat lengths within the androgen receptor gene.

## Racial Variation in CAG Repeat Lengths Within the Androgen Receptor Gene Among Prostate Cancer Patients of Lower Socioeconomic Status

CHARLES BENNETT, DOUGLAS PRICE, SIMON KIM, DACHAO LIU, BORKO JOVANOVIC, DEREK NATHAN, MARGARET JOHNSON, JEFFREY MONTGOMERY, KELLY CUDE, JUSTIN BROCKBANK, OLIVER SARTOR, WILLIAM FIGG

**Abstract:** To evaluate (1) whether there were racial differences in the androgen receptor gene CAG repeat length and in clinical or laboratory attributes of prostate cancer at the time of diagnosis; (2) whether there were differences in race, Gleason score, prostate-specific antigen (PSA) level, and stage at diagnosis by androgen receptor gene CAG repeat length; and (3) whether sociodemographic, clinical, and laboratory based factors might be associated with advanced-stage prostate cancer. To our knowledge, this study is the first to report on CAG repeat lengths in a cohort of prostate cancer patients, which includes large numbers of African-American men.

CAG repeat lengths on the androgen receptor gene were evaluated for 151 African-American and 168 white veterans with prostate cancer. The $x^2$ test, *t* test, and logistic regression analyses were used to evaluate the associations between CAG repeat lengths and race, stage, histologic grade, and PSA levels at diagnosis.

The mean age of the cohort at the time of diagnosis was 68.7 years. In this cohort of men with prostate cancer, short CAG repeat length on the androgen receptor gene was associated with African-American race and possibly with higher stage but not with other clinical or pathologic findings.

*(J Clin Oncol 20:3599-3604, 2002)*
*ERIC Durham, NC*

# CSP #97-010

# Reflux Disease

This study assessed whether endoscopy to detect disease in the esophagus reduces mortality from adenocarcinoma of the esophagus or gastric cardia for patients with gastroesophageal reflux.

## A Case-Control Study of Endoscopy and Mortality from Adenocarcinoma of the Esophagus or Gastric Cardia in Persons with GERD

KEARNEY DJ, CRUMP C, MAYNARD C, BOYKO EJ

**Abstract:** *Background*: This study assessed whether EGD reduces mortality from adenocarcinoma of the esophagus or gastric cardia for patients with gastroesophageal reflux.

*Methods*: A case-control study was performed. A total of 245 incident cases of death caused by adenocarcinoma of the esophagus or gastric cardia (1995-1999) in which reflux was present were identified using Veterans Health Administration databases. A total of 980 controls with reflux but no death from adenocarcinoma were frequency matched for age, gender, and race. The occurrences of EGD from 1990 onward were compared for cases and controls. Logistic regression analysis with adjustment for potential confounding factors was performed.

*Results*: All the subjects were men. Cases were significantly less likely to have had an EGD in the time period of interest as compared with controls (adjusted odds ratio 0.66: 95% CI [0.45, 0.96], p = 0.03). This negative association was as strong for any EGD performed within 1 to 8 years before diagnosis as for a more recent EGD. However, there were no controls that included esophagectomy and no controls with a nonfatal diagnosis of adenocarcinoma, raising the question of whether EGD and reduced mortality are causally linked. The risk of dying from adenocarcinoma was significantly lower for men with a diagnosis of GERD as an inpatient relative to men in whom the diagnosis was made as an outpatient (adjusted odds ratio 0.21: 95% CI [0.15, 0.31], p < 0.01).

*Conclusions*: For patients with GERD, performing an EGD is associated with reduced mortality from adenocarcinoma of the esophagus or gastric cardia, but whether this is a causative association remains unclear.

*(Gastrointest Endosc 57:823-829, 2003)*
*ERIC Seattle, WA*

# CSP #362

# Oral Anticoagulant Therapy to Improve Patency of Small Caliber Prosthetic Bypass Grafts

Thromboembolic events, most commonly in the form of deep venous thrombosis, pulmonary embolism, myocardial infarction or stroke, cause considerable yearly mortality and morbidity. Three genetic mutations have been associated with an increased risk of thromboembolic events. There are factor V Leiden R506Q, prothrombin G20210A, and methylenetetrahydrofolate reductase C677T (MTHFR) mutations. The purpose of this study was to determine the effect of these mutations on patency of peripheral bypass grafts and preoperative and postoperative thromboembolic events in 244 randomly selected volunteers participating in VA Cooperative Study #362, "Oral Anticoagulant Therapy to Improve Patency of Small Caliber Prosthetic Bypass Grafts." These patients had been randomized to receive either aspirin therapy or aspirin and warfarin therapy after a peripheral bypass procedure. Patients with the various mutations were compared for graft patency and preoperative and postoperative thromboembolic events. Patients with either factor V Leiden or prothrombin mutations were not at increased risk for postoperative graft occlusion or thromboembolic events. Patients heterozygous for MTHFR had a lower risk of graft thrombosis and higher (better) graft patency rates compared to both homozygous and wild-type control patients. Thus, screening for the MTHFR gene mutation before surgery may identify patients at increased risk of graft thrombosis.

## Can Screening for Genetic Markers Improve Peripheral Artery Bypass Patency?

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**Abstract**: *Objective*: Three genetic mutations have been associated with an increased risk of thromboembolic events: factor V Leiden R506Q, prothrombin G20210A, and methylenetetrahydrofolate reductase C677T (MTHFR) mutations. The aim of this study was to determine the effect of these mutations on patency of peripheral bypass procedures and preoperative and postoperative thromboembolic events.

*Methods*: Two hundred forty-four randomly selected volunteers participating in the Veterans Affairs Cooperative Study #362 were tested for factor V Leiden, prothrombin, or MTHFR mutations with polymerase chain reaction. Patients enrolled in the study were randomized to receive aspirin therapy or aspirin and warfarin therapy after a peripheral bypass procedure. The frequencies of preoperative and postoperative

thromboembolic events and primary patency (PP), assisted primary patency (APP), and secondary patency (SP) rates were compared among carriers of the various mutations.

*Results*: Fourteen patients (5.7%) were heterozygous for the factor V Leiden mutation, seven (2.9%) were heterozygous for the prothrombin mutation, and 108 (44.6%) were heterozygous and 15 (6.2%) homozygous for the MTHFR mutation. After surgery, patients homozygous for the MTHFR gene mutation had increased graft thrombosis, compared with patients who were heterozygous (33.3% versus 11.1%; P = .01), and lower PP, APP and SP rates (P < .05). Furthermore, patients heterozygous for the MTHFR mutation had fewer graft thromboses (11.1% versus 24.4%; P = .01), fewer below-knee amputations (0.9% versus 7.6%; P = .02), and higher PP, APP, and SP rates (PP, 79.6%; APP, 88.9%; SP, 90.7%; P < .05) compared with wild-type control subjects (PP, 63%; APP, 75.6%; SP, 76.5%; P < .05).

*Conclusion*: Patients with either factor V Leiden or prothrombin mutations were not at an increased risk for postoperative graft occlusion or thromboembolic events. Patients heterozygous for MTHFR mutation had a lower risk of graft thrombosis and higher graft patency rates compared with both homozygous and wild-type control subjects. Patients homozygous for the MTHFR mutation had lower graft patency rates compared with patients who were heterozygous, and a trend was seen toward lower patency rates compared with wild-type control subjects. Therefore, screening for the MTHFR gene mutation before surgery may identify patients at an increased risk of graft thrombosis.

*(J Vasc Surg 36:1198-1206, 2002)*
*CSPCC Perry Point, MD*

# CSP #363

# The VA HDL Intervention Trial (HIT): Secondary Prevention of Coronary Heart Disease in Men with Low HDL-Cholesterol and Desirable LDL-Cholesterol

VA-HIT was a large heart study that enrolled 2531 patients from 20 VA medical centers nationwide between 1991 to 1998. Patients with heart disease and low levels of HDL cholesterol and normal levels of LDL cholesterol were given either a drug called gemfibrozil or placebo. The results of the study were that gemfibrozil reduced heart attacks and heart-related deaths by 22% and reduced strokes by 25%.

Article #1: Since about one-fourth of the VA-HIT patients had diabetes and many were overweight, a sub-study was conducted to determine if these patients were more prone to heart attack, heart-related deaths, and to stroke. This study found that this group of patients had almost twice the chance of having one of these heart-related events occur. Also, the study drug gemfibrozil was more effective in reducing these heart-related events in diabetics and in patients with high insulin levels whether or not they had diabetes.

Article #2: This sub-study examined whether insulin resistance was related to heart attack, stroke, or heart-related death and found that patients with the highest insulin resistance (the worst levels) had a 50% higher chance of having one of these events occur. The findings suggest that insulin resistance is more important than either HDL or LDL cholesterol in assessing the risk of heart-related events in these patients.

## Diabetes, Plasma Insulin, and Cardiovascular Disease

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**Abstract:** *Background*: Diabetes mellitus, impaired fasting glucose level, or insulin resistance are associated with increased risk of cardiovascular disease.

*Objectives:* To determine the efficacy of gemfibrozil in subjects with varying levels of glucose tolerance or hyperinsulinemia and to examine the association between diabetes status and glucose and insulin levels and risk of cardiovascular outcomes.

*Methods:* Subgroup analyses from the Department of Veterans Affairs High-Density Lipoprotein Intervention Trial, a randomized controlled trial that enrolled 2531 men with coronary heart disease (CHD), a high-density lipoprotein cholesterol level of 40 mg/dL or less ($\leq$1.04 mmol/L) and a low-density lipoprotein cholesterol level of 140 mg/dL or less ($\leq$3.63 mmol/L). Subjects received either gemfibrozil (1200 mg/d) or

matching placebo and were followed up for an average of 5.1 years. In this article, we report the composite end point (CHD death, stroke, or myocardial infarction).

*Results:* Compared with those with a normal fasting glucose level, risk was increased in subjects with known diabetes (hazard ratio [HR], 1.87; 95% confidence interval [CI], 1.44-2.43; P=.001) and those with newly diagnosed diabetes (HR, 1.72; 95% CI, 1.10-2.68; P=.02). In persons without diabetes, a fasting plasma insulin level of 39 μU/mL or greater (≥271 pmol/L) was associated with a 31% increased risk of events (P=.03). Gemfibrozil was effective in persons with diabetes (risk reduction for composite end point, 32%; P=.004). The reduction in CHD death was 41% (HR, 0.59; 95% CI, 0.39-0.91; P=.02). Among individuals without diabetes, gemfibrozil was most efficacious for those in the highest fasting plasma insulin level quartile (risk reduction, 35%, P=.04).

*Conclusion:* In men with CHD and a low high-density lipoprotein cholesterol level, gemfibrozil use was associated with a reduction in major cardiovascular events in persons with diabetes and in nondiabetic subjects with a high fasting plasma insulin level.

*(Arch Intern Med 162: 2597-2604, 2002)*
*CSPCC West Haven, CT*

# Insulin Resistance and Cardiovascular Events with Low HDL Cholesterol
# The Veterans Affairs HDL Intervention Trial (VA-HIT)

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**Abstract:** *Objective:* To assess the effect of insulin resistance and the benefit of the fibrate, gemfibrozil, on the incidence of major cardiovascular events in subjects with low HDL cholesterol and a broad range of triglyceride values who participated in the Veterans Affairs High Density Lipoprotein Intervention Trial (VA-HIT).

*Research Design and Methods:* This intention-to-treat analysis, specified as a secondary objective in VA-HIT, determined using Cox proportional hazards models the 5-year combined incidence of nonfatal myocardial infarction, coronary heart disease (CHD) death, or stroke in relation to the presence or absence of insulin resistance (defined by the highest tertile of the homeostasis model assessment of insulin resistance, HOMA-IR) in conjunction with lower and higher levels of HDL cholesterol and triglycerides. The study population consisted of 2,283 men with known coronary heart disease (CHD), treated with either placebo or gemfibrozil, who could be subdivided into groups with diabetes with or without insulin resistance, with no diabetes but insulin resistance, and with neither diabetes nor insulin resistance.

*Results:* With insulin resistance there was a significantly higher relative risk (RR) of a cardiovascular event both with diabetes (RR of 1.62 with 95% CI of 1.28-2.06) and without diabetes (RR of 1.43 with 95% CI of 1.03-1.98) than without insulin resistance. Throughout both lower and higher ranges of HDL cholesterol and triglycerides, the rate of new cardiovascular events and the reduction of events with gemfibrozil was greater in subjects with insulin resistance than without, despite the finding that an increase in HDL cholesterol and a decrease in triglycerides with gemfibrozil was less with insulin resistance than without insulin resistance.

*Conclusions:* Results show that in VA-HIT the occurrence of a new cardiovascular event and the benefit of fibrate therapy was much less dependent on levels of HDL cholesterol or triglycerides than on the presence or absence of insulin resistance.

*(Diabetes Care 26(5):1513-1517, 2003)*
*CSPCC West Haven, CT*

# CSP #385

## Urgent Revascularization in Unstable Angina

Patients with unstable chest pain due to clogged coronary arteries who cannot be helped with drug therapy represent some of the most challenging patients to cardiologists and cardiac surgeons. How these patients are treated often depends on the interests, skills and biases of physicians at a particular medical center. The hypothesis of this study is that initial treatment with percutaneous coronary intervention is a viable alternative to CABG in this patient population. Over a 5 year period, 2,432 eligible patients were entered into the study. Of these, 454 were randomized and 1977 were followed in a registry. The registry consisted of two subgroups; patients whose therapy was physician-directed and patients whose therapy was directed by patient-choice.

Article #1: Reports the long-term survival of 760 revascularized patients in the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) randomized trial and registry, who had at least one prior CABG.

Article #2: Compares long-term survival after percutaneous coronary intervention or coronary artery bypass graft surgery for the treatment of diabetics with medically refractory unstable angina. The trial demonstrated similar 36- month survival.

Article #3: Compares six-month health related quality of life (HRQL) after percutaneous coronary intervention or coronary artery bypass graft surgery for the treatment of high risk, medically refractory unstable angina. The trial demonstrated similar six-month HRQL.

# Percutaneous Coronary Intervention Versus Repeat Bypass Surgery for Patients With Medically Refractory Myocardial Ischemia

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**Abstract:** *Objectives:* This report compares long-term percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) survival among post-CABG patients included in the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) randomized trial and prospective registry.

*Background:* Repeat CABG surgery is associated with a higher risk of mortality than first-time CABG. The AWESOME is the first randomized trial comparing CABG with PCI to include post-CABG patients.

*Methods:* Over a five-year period, patients at 16 hospitals were screened to identify a cohort of 2,431 individuals who had medically refractory myocardial ischemia and at least one of five high-risk factors. There were 454 patients in the randomized trial, of whom 142 had prior CABG. In the physician-directed registry of 1,650 patients, 719 had prior CABG. Of the 327 patient-choice registry patients, 119 had at least one prior CABG. The CABG and PCI survivals for the three groups were compared using Kaplan-Meier curves and log-rank tests.

*Results:* The CABG and PCI three-year survival rates were 73% and 76% respectively for the 142 randomized patients. In the physician-directed registry, 155 patients were assigned to reoperation and 357 to PCI. In the patient-choice registry, 32 patients chose reoperation, and 74 chose PCI; 36-month survivals were 65% and 86%, respectively.

*Conclusion:* Percutaneous coronary intervention is preferable to CABG for many post-CABG patients.

*(J Am Coll Cardiol 40:1951-4, 2002)*
*CSPCC Hines, IL*

# Percutaneous Coronary Intervention Versus Coronary Bypass Graft Surgery for Diabetic Patients With Unstable Angina and Risk Factors for Adverse Outcomes With Bypass

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**Abstract:** *Objectives:* This study compared survival after percutaneous coronary intervention (PCI) with survival after coronary artery bypass graft surgery (CABG) among diabetics in the Veterans Affairs AWESOME (Angina With Extremely Serious Operative Mortality Evaluation) study randomized trial and registry of high-risk patients.

*Background:* Previous studies indicate that CABG may be superior to PCI for diabetics, but no comparisons have been made for diabetics at high risk for surgery.

*Methods:* Over five years (1995-2000), 2,431 patients with medically refractory myocardial ischemia and at least one of five risk factors (prior CABG, myocardial infarction within seven days, left ventricular ejection fraction <0.35, age >70 years, or an intra-aortic balloon being required to stabilize) were identified. A total of 781 were acceptable for CABG and PCI, and 454 consented to be randomized. The 1,650 patients not acceptable for both CABG and PCI constitute the physician-directed registry, and the 327 who were acceptable but refused to be randomized constitute the patient-choice registry. Diabetes prevalence was 32% (144) among randomized patients, 27% (89) in the patient-choice registry, and 32% (525) in the physician-directed registry. The CABG and PCI survival rates were compared using Kaplan-Meier curves and log-rank tests.

*Results:* The respective CABG and PCI 36-month survival rates for diabetic patients were 72% and 81% for randomized patients, 85% and 89% for patient-choice registry patients, and 73% and 71% for the physician-directed registry patients. None of the differences was statistically significant.

*Conclusions:* We conclude that PCI is a relatively safe alternative to CABG for diabetic patients with medically refractory unstable angina who are at high risk for CABG.

*(J Am Coll Cardiol 40:1555-66, 2002)*
*CSPCC Hines, IL*

# Health-Related Quality of Life After Percutaneous Coronary Intervention Versus Coronary Bypass Surgery in High-Risk Patients With Medically Refractory Ischemia

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**Abstract:** *Objectives:* We compared six-month health-related quality of life (HRQL) for high-risk patients with medically refractory ischemia randomized to percutaneous coronary intervention (PCI) versus coronary artery bypass graft (CABG) surgery.

*Background:* Mortality rates after PCI and CABG surgery are similar. Therefore, differences in HRQL outcomes may help in the selection of a revascularization procedure.

*Methods:* Patients were enrolled in a Veterans Affairs multicenter randomized trial comparing PCI versus CABG for patients with medically refractory ischemia and one or more risk factors for adverse outcome; 389 of 423 patients (92%) alive six months after randomization completed a Short Form-36 (SF-36) health status survey. Primary outcomes were the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores from the SF-36. Multivariable analyses were used to evaluate whether PCI or CABG surgery was associated with better PCS or MCS scores after adjusting for over 20 baseline variables.

*Results:* There were no significant differences in either PCS scores (38.7 vs. 37.3 for PCI and CABG, respectively; p=0.23) or MCS scores (45.5 vs. 46.1, p= 0.58) between the treatment arms. In multivariable models, there remained no difference in HRQL for post-PCI versus post-CABG patients (for PCS, absolute difference = 0.56 ± standard error of 1.14, p = 0.63; for MCS, absolute difference = -1.23 ± 1.12, p = 0.27). We had 97% power to detect a four-point difference in scores, where four to seven points is a clinically important difference.

*Conclusions:* High-risk patients with medically refractory ischemia randomized to PCI versus CABG surgery have equivalent six-month HRQL. Therefore, HRQL concerns should not drive decision making regarding selection of a revasculari-zation procedure for these patients.

*(J Am Coll Cardiol 41:1732-8, 2003)*
*CSPCC Hines, IL*

# CSP #399

## The Effects of Antiarrhythmic Therapy in Maintaining Stability of Sinus Rhythm in Atrial Fibrillation

Atrial fibrillation (AF) is now the most common cardiac arrhythmia encountered in clinical practice, leading to significant mortality and morbidity. It affects 1.0 to 1.5 million Americans and is responsible for more than 75,000 strokes a year. In people 70 years or older, the prevalence rate is more than 3.5%, and the condition can involve as many as 40% of patients with congestive heart failure. It is an established risk factor for congestive heart failure and stroke and other embolic phenomena; it impairs exercise capacity, and may produce disabling palpitations and other associated symptoms. Atrial fibrillation is the basis for hospitalization twice as often as all other arrhythmias combined, and six times as often as ventricular tachycardia/fibrillation. The average hospital stay for atrial fibrillation is five days. The best approach to standardized therapy for atrial fibrillation remains to be developed. The main goals of treatment are to relieve symptoms (usually due to a fast heart rate), prevent the development of stroke, and improve functional capacity. Symptoms may be relieved by slowing the ventricular response or restoring and maintaining sinus rhythm. The incidence of stroke is reduced by anticoagulation or restoring sinus rhythm, which may also improve the patient's functional capacity. It is likely that maintenance of sinus rhythm (SR) may preclude the necessity for anticoagulation, which as a form of therapy is not tolerated or is contraindicated in more than 30% of patients. Thus, the maintenance of sinus rhythm in patients predisposed to atrial fibrillation is a major therapeutic goal, and agents that are effective in this regard are very important. This study compares the efficacy of two of the most promising agents, amiodarone and sotalol, to that of placebo in maintaining sinus rhythm in patients with atrial fibrillation who either spontaneously convert to sinus rhythm or are converted by chemical or electrical cardioversion.

This article reports the primary and secondary objectives and study design.

# Comparison of Sotalol Versus Amiodarone in Maintaining Stability of Sinus Rhythm in Patients With Atrial Fibrillation (Sotalol-Amiodarone Fibrillation Efficacy Trial [Safe-T])

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**Abstract:** The Sotalol-Amiodarone Fibrillation Efficacy Trial (SAFE-T) is a randomized, double-blind, multicenter, placebo-controlled trial in which the effects of sotalol and amiodarone in maintaining stability of sinus rhythm are being examined in patients with persistent atrial fibrillation at 20 Veterans Affairs medical centers. The time to the occurrence of atrial fibrillation or flutter in patients with atrial fibrillation converted to sinus rhythm is the primary outcome measure, with a number of parameters as secondary end points. SAFE-T had randomized 665 patients when enrollment terminated on October 31, 2001. Follow-up of patients continued until October 31, 2002, for a maximum period of 54 months and a minimum period of 12 months for all patients.

*(Am J Cardiol 92:468-472, 2003)*
*CSPCC Hines, IL and CSP CRPCC Albuquerque, NM*

# CSP #440

# Anti-Thrombotic Agents in the Prevention of Hemodialysis Access Thrombosis

The hemodialysis access graft thrombosis prevention study compared the effectiveness of aspirin plus clopidogrel (active treatment) to placebo for prevention of thrombosis in hemodialysis access grafts in patients with chronic kidney disease. The study was conducted at 30 hemodialysis units at VA medical centers between December 1998 and October 1999; 200 participants were randomized, 96 to placebo and 104 to the active combination group. The study was originally designed to enroll 320 veterans over a period of 6 months, and minimum follow-up time was to be two years.

The study was stopped by the Data and Safety Monitoring Board after one year because of significantly increased bleeding in the active treatment arm – 23 participants in the placebo group and 44 participants in the active treatment group experienced a bleeding event. There was no significant benefit of active treatment in the prevention of hemodialysis graft thrombosis.

## Randomized Controlled Trial of Clopidogrel plus Aspirin to Prevent Hemodialysis Access Graft Thrombosis

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**Abstract:** Thrombosis of hemodialysis vascular access grafts represents a major medical and economic burden. Experimental and clinical models suggest a role for antiplatelet agents in the prevention of thrombosis. The study was designed to determine the efficacy of the combination of aspirin and clopidogrel in the prevention of graft thrombosis. The study was a randomized, double-blind trial conducted at 30 hemodialysis units at Veterans Affairs medical centers. Participants undergoing hemodialysis with a polytetrafluoroethylene graft in the arm were randomized to receive either double placebos or aspirin (325 mg) and clopidogrel (75 mg) daily. Participants were to be monitored while receiving study medications for a minimum of 2 yr. The study was stopped after randomization of 200 participants, as recommended by the Data and Safety Monitoring Board because of a significantly increased risk of bleeding among the participants receiving aspirin and clopidogrel therapy. The cumulative incidence of bleeding events was significantly greater for those participants, compared with participants receiving placebos [hazard ratio, 1.98; 95% confidence interval (CI), 1.19 to 3.28; P=0.007]. Twenty-three participants in the placebo group and 44

participants in the active treatment group experienced a bleeding event (P=0.006). There was no significant benefit of active treatment in the prevention of thrombosis (hazard ratio, 0.81; 95% CI, 0.47 to 1.40; P=0.45), although there was a trend toward a benefit among participants who had not experienced previous graft thrombosis (hazard ratio, 0.52; 95% CI, 0.22 to 1.26; P=0.14). In the hemodialysis population, therapy with aspirin and clopidogrel was associated with a significantly increased risk of bleeding and probably would not result in a reduced frequency of graft thrombosis.

*(J Am Soc Nephrol 14: 2313-2321, 2003)*
*CSPCC West Haven, CT*

# CSP #995

# Trial to Evaluate the Effect of Digitalis on Mortality in Heart Failure (VA-NHLBI)

The incidence and prevalence of heart failure increases with advancing age. However, there is limited data on the clinical course and response to specific therapeutic interventions in elderly patients with heart failure. This study was designed to determine the effect of increasing use on mortality, hospitalization and digoxin side effects, as well as the effect of digoxin on clinical outcomes as a function of age. It was determined that, in patients with heart failure, the beneficial effects of digoxin in reducing all cause and heart failure hospitalizations, as well as heart failure death or hospitalization are independent of death. Thus digoxin remains a useful drug for heart failure patients of all ages.

## Determination of Vital Status at the End of the DIG Trial

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**Abstract:** The Digitalis Investigation Group (DIG) trial was a randomized, double-blind placebo-controlled trial whose primary objective was to determine whether digoxin had beneficial, harmful, or no effect on total mortality in patients with heart failure who were in sinus rhythm and whose ejection fraction was ≤0.45. The study was designed as a large simple trial with a large number of centers (302) in the United States and Canada, many of which were research inexperienced. To ensure that the results of the trial would be reported accurately without possible bias due to missing data, the study leadership decided that no outcome results would be reported until the vital status at the end of the study was known for at least 97% of the study participants. Planning for closeout of the study began a year prior to the common end date of December 31, 1995 and included plans for obtaining vital status on December 31, 1995. Participants were given postcards at their final study visit to be completed and mailed on or after January 1, 1996. Of 5602 postcards distributed, 5070 (90.5%) were completed and returned. A contract search agency was hired to locate the remaining participants. Of the total 7788 participants entered into the DIG trial, only 97 participants (1.2%) could not have their vital status as of December 31, 1995 determined. It is recommended that investigators having an outcome measure with a common end date include plans in their protocols for obtaining their measures and activate those plans as early as possible during the course of the study.

*(Control Clin Trials 24:26-730, 2003)*
*CSPCC Perry Point, MD*

## Overview of the DIG Trial

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**Abstract:** Congestive heart failure is a major public health problem in the United States, Canada, and other Western countries. The Digitalis Investigation Group (DIG) trial was a randomized, double-blind placebo-controlled trial that evaluated the effects of digoxin on all-cause mortality and on hospitalization for heart failure in patients with heart failure and left ventricular ejection fraction <0.45 with normal sinus rhythm. It was designed as a large simple trial. There were 6800 patients entered into the main study over a 31.5-month recruitment period at 302 participating centers in the United States and Canada. All patients were followed for a minimum of 28 months. In order for this study to succeed, many groups had to work together successfully. In this supplement, we present practical aspects of organizing and conducting a large simple trial such as DIG.

*(Control Clin Trials 24:269S-276S, 2003)*
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## The Role of the Data Coordinating Center in the DIG Trial

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**Abstract:** The Digitalis Investigation Group (DIG) trial was a large simple trial (LST) begun in 1990 as a collaboration between the National Heart, Lung, and Blood Institute and the Department of Veterans Affairs Cooperative Studies Program (VA CSP). Its primary objective was to determine whether digitalis had beneficial, harmful, or no effect on total mortality in patients with congestive heart failure and an ejection fraction of ≤ 0.45. The Perry Point VA CSP Coordinating Center served as the trial's data coordinating center (DCC). The DCC was involved in all phases of the study from planning and design, organizational and start-up, patient recruitment and follow-up, through closeout, final analyses, and manuscript preparation. While DCC responsibilities for an LST are basically the same as for other multicenter randomized clinical trials, its size and the inclusion of many inexperienced research sites can add a complexity that the DCC must be prepared to handle from the beginning. This paper describes the role of the DCC in the DIG trial.

*(Control Clin Trials 24:277S-288S, 2003)*
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# The Role of the Pharmacy Coordinating Center in the DIG Trial

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**Abstract:** Large simple trials (LSTs) emerged in response to the need for large sample sizes to answer important clinical questions in which treatments have a moderate effect on clinical endpoints. Between 1991 and 1996 the National Heart, Lung, and Blood Institute and the Department of Veterans Affairs (VA) Cooperative Studies Program conducted a LST entitled "Digitalis Investigation Group (DIG): Trial to Evaluate the Effect of Digitalis on Mortality in Heart Failure." The VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center served as the DIG pharmacy coordinating center (PCC). As a direct result of involvement in the DIG trial, the PCC identified the need for an increased emphasis on computerization and automated support of clinical trials, especially LSTs.

*(Control Clin Trials 24:289S-297S, 2003)*
*CSP CRPCC, Albuquerque, NM and CSPCC Perry Point, MD*

# The Use of Regional Coordinating Centers in Large Clinical Trials: the DIG Trial

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**Abstract:** The Digitalis Investigation Group (DIG) trial was a large simple clinical trial that involved 302 participating centers in the United States and Canada. In order to encourage participation by Canadian investigators, to provide additional help to what were expected to be largely research-inexperienced investigators in Canada, and to provide the study's data coordinating center with resources in Canada to deal with potentially different rules, regulations, and cultural differences, regional coordinating centers were established in four regions of Canada: the Maritime Provinces, Quebec, Ontario, and Western Canada. Canadian centers recruited significantly better than their U.S. counterparts and had slightly better retention and follow-up. While it is not possible to declare that the regional coordinating centers were responsible for this improvement, it is believed that these regional centers did play a role. This role included being able to identify investigators who could be expected to do well, providing one-on-one training and instruction to investigators, and being able to solve problems and implement change in the relatively fewer centers in their regions. The regional coordinating center also reduced the intensity of the workload on the data coordinating center by serving as the primary point of contact for Canadian investigators. The use of regional coordinating centers in studies with a large number of participating centers is highly recommended.

*(Control Clin Trials 24:298S-305S, 2003)*
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# The Role of the Data Coordinating Center in the IRB Review and Approval Process: the DIG Trial Experience

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**Abstract:** Before any clinical trial can begin to recruit patients, participating clinical centers must obtain approval from their institutional review board (IRB). When studies are federally funded, such as by the U.S. Department of Health and Human Services (DHHS), centers must also have or obtain a federal compliance agreement from the Office of Human Research Protections (formerly the Office for Protection from Research Risks [OPRR]). The Digitalis Investigation Group (DIG) trial was a large, international, double-blind, DHHS-funded randomized trial on the effect of digoxin on mortality in heart failure. Due to the anticipated number of centers (>200), the study's data coordinating center (DCC) was requested to assume additional responsibilities that included: (1) act as a liaison between the OPRR and all study centers; (2) review and correct all assurance statements before submission to the OPRR; (3) review and approve all centers' informed consent forms; and (4) help the many research-inexperienced centers to establish IRBs or to locate an IRB in their region that would accept IRB responsibility for them. Although a heavy burden was placed on the DCC, the IRB and OPRR approval process was probably shortened by many weeks at those centers not already possessing a federal compliance agreement. This enabled the study to be completed on schedule and within budget.

*(Control Clin Trials 24:306S-315S, 2003)*
*CSPCC Perry Point, MD*

# Lessons Learned from the DIG Trial

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**Abstract:** The Digitalis Investigation Group (DIG) trial was the first large simple trial conducted by the National Heart, Lung, and Blood Institute in conjunction with the Department of Veterans Affairs. A large simple trial is a major undertaking. Simplification at the sites requires careful planning and discipline. Lessons learned from the DIG trial were (1) keep a large simple trial very simple and keep all study procedures very simple, (2) ancillary studies are important and can complement a large simple trial, but require careful advanced planning, (3) anticipate special needs when shipping study drugs internationally, (4) regional coordinating centers can be very useful, (5) recruit as many capable sites as possible, (6) provide research-inexperienced sites/investigators with extra help to obtain federalwide assurance statements from the Office for Human Research Protections and institutional review board approvals, (7) adequately reimburse sites for the work completed, (8) maintain investigator enthusiasm, (9) monitor the slow performers and sites with numerous personnel changes, (10) choose an endpoint that is easy to ascertain, (11) keep the trial simple for participants, and (12) plan early for closeout and for activities between the end of the trial and publication of results.

*(Control Clin Trials 24:316S-326S, 2003)*
*CSPCC Perry Point, MD*

The VA Cooperative Studies Program as part of CSP #995 conducted a pre-specified sub-study to evaluate the effect of digoxin therapy on health-related quality of life in patients with heart failure. In a subset of 589 patients out of the total DIG study population of 7,788, digoxin therapy had no effect on health-related quality of life, despite the fact that this group was comparable to the remaining study patients in age and other baseline clinical measures.

## The Effect of Digoxin on the Quality of Life in Patients with Heart Failure

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**Abstract**: *Background*: The Digitalis Investigation Group (DIG) trial was a randomized double-blind placebo-controlled study that examined the effect of digoxin on mortality in 7,788 patients with heart failure and sinus rhythm. A prespecified substudy evaluated the effect of digoxin therapy on health-related quality of life (HQOL) in a subset of these patients.

*Methods:* Patients in the DIG trial had clinical heart failure and were randomized to either digoxin or placebo in addition to their baseline diuretic and angiotensin-converting enzyme therapy (n = 7,788). The patients in this substudy had HQOL measured using a self-administered questionnaire employing scales that measured general health, physical functioning, depression, anger, anxiety, life satisfaction, and disease specific measures. A subjective assessment by the investigator and a 6-minute walk test evaluated functional status. HQOL was measured at baseline and at the 4- and 12-month follow-up visits.

*Results*: The baseline characteristics of the patients in the quality of life substudy (n = 589) were comparable to the remaining patients in the study ( n = 7,199) by age and other clinical measures, including history of prior myocardial infarction or etiology of heart failure; heart failure was of shorter duration and the ejection fraction was slightly better than in the main trial. Within the substudy, patients receiving digoxin (n = 298) or placebo (n = 291) were also similar in baseline characteristics. There was no statistically significant difference in any HQOL measure between the digoxin and the placebo groups at baseline. At the 4-month visit, only perceived health was improved in the digoxin group. At 12 months, there was no statistically significant difference in perceived health, physical functioning, Minnesota Living with Heart Failure, depression, anxiety, anger, Ladder of Life, or the 6-minute walk between the digoxin and placebo groups.

*Conclusion*: In this subset of the DIG population, digoxin therapy had no effect on the HQOL in patients with heart failure and sinus rhythm.

*(Journal of Cardiac Failure 9(1):4-12, 2003)*
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# CSP #97-010

# Carotid Artery Disease

This work is part of a large study of risk factors for carotid artery disease. Carotid artery disease is a major cause of stroke and people with carotid artery disease also tend to have heart disease. We are evaluating many genetic and environmental factors that interact to cause disease. A major focus is the enzyme paraoxonase.

Paraoxonase is a protein that breaks down oxidized cholesterol molecules. We showed earlier that paraoxonase activity was lower in subjects with heart disease. Here we showed that vitamins C and E in the diet was associated with increased paraoxonase activity.

## Vitamin C and E Intake is Associated with Increased PON1 Activity

JARVIK GP, TSAI NT, MCKINSTRY LA, WANI R, BROPHY VH, RICHTER RJ, SCHELLENBERG GD, HEAGERTY PJ, HATSUKAMI TS, FURLONG CE

**Abstract**: *Objective*: Paraoxonase (PON1), an esterase physically associated with high-density lipoprotein, has been shown to inhibit atherogenic low-density lipoprotein and high-density lipoprotein oxidation. PON1 activity appears to be primarily under genetic control with some environmental modification and is a predictor of vascular disease. Vitamins C and E, dietary antioxidants, scavenge free-oxygen radical products that may depress PON1 activity. Therefore, we evaluated the relationship between dietary vitamin C and E intake and PON1 activity.

*Methods and Results*: The vitamin C and E intakes of male white subjects (n=189) were estimated by using a standardized food frequency survey. With covariates, vitamin C or E intakes were found to be significant positive predictors of PON1 activity for the hydrolysis of paraoxon and diazoxon with the use of linear regression. Smoking and use of statins were independent predictors of PON1 activity.

*Conclusions*: PON1 activity, which is primarily genotype dependent, varies with antioxidant vitamins, cigarette smoking, and statin drug use. Because PON1 activity is a better predictor of vascular disease than is the currently described genetic variation in PON1, further studies of the environmental influences on PON1 activity and additional PON1 genetic variants are warranted.

*(Arterioscl Throm Vas 22:1329-1333, 2002)*
*ERIC Seattle, WA*

This work is part of a large study of risk factors for carotid artery disease. We are evaluating many genetic and environmental factors that interact to cause disease. A major focus is the enzyme paraoxonase. We found new changes that altered the function of the paraoxonase gene.

## Novel Paraoxonase (PON1) Nonsense and Missense Mutations Predicted by Functional Genomic Assay Of PON1 Status

JARVIK GP, JAMPSA R, RICHTER RJ, CARLSON CS, RIEDER MJ,
NICKERSON DA, FURLONG CE

**Abstract:** Paraoxonase (PON1) has been termed an environmental response enzyme for its function in the detoxification of organophosphate pesticides, nerve agents and pharmaceuticals such as glucocorticoids and statins, as well as its cardioprotective role in breaking down oxidized LDL. PON1 (192) genotype can be predicted with high accuracy from an examination of the two-dimensional plot of paraoxon and diazoxon hydrolysis rates. Individuals for whom this functional genomic assay failed to predict PON1(192) genotype, or who had a low PON activity relative to others with the same genotype, were predicted to have genetic alterations that explained the inconsistency. Sequencing of the PON1 region of 23 Caucasian individuals detected a nonsense mutation changing amino acid 194 from a Trp to a stop codon (PON1(Trp194stop)). It was predicted that subjects who genotyped as PON1(192QR) but phenotyped as PON1(192QQ) or PON1(192RR) might carry the protein truncation mutation for which the defective product failed to be detected by the phenotyping assay. Screening of the five discordant subjects resulted in the detection of a single Caucasian carrying the stop codon, and determined its phasing on the PON1(192R) allele. Sequencing confirmed the change and revealed an additional subject with a likely deletion of the 5' end of the PON1 gene. Additional sequencing of 25 subjects with low PON1 activities identified two additional previously undescribed PON1 mutations, which may affect PON1 function: PON1(Pro90Leu) associated with the PON1(192Q) allele and PON1(Asp124missplice) associated with the PON1(192R) allele.

*(Pharmacogenetics 13:1-5, 2003)*
*ERIC Seattle, WA*

We found that using the complex structure of changes in the paraoxonase gene, called haplotype, did not improve our ability to predict who has vascular disease once paraoxonase activity was known.

## Paraoxonase Activity, but not Haplotype Utilizing the Linkage Disequilibrium Structure, Predicts Vascular Disease

JARVIK GP, HATSUKAMI TS, CARLSON CS, RICHTER RJ, JAMPSA R, BROPHY VH, MARGOLIN S, RIEDER MJ, NICKERSON DA, SCHELLENBERG GD, HEAGERTY PJ, FURLONG CE

**Abstract:** *Objective*: The effects of paraoxonase (PON1) activity and of genetic variation in the PON1 promoter and coding region on carotid artery disease (CAAD) were investigated.

*Methods and Results*: We identified functional promoter polymorphisms and examined their effects in a cohort with and without CAAD. We used the full sequences in 23 white subjects to determine the linkage disequilibrium (LD) structure of the PON1 region and to direct the grouping of haplotypes for disease association testing. There are several discrete regions of the PON1 gene with strong local LD, but the useful levels of LD do not extend across the entire gene. Indeed, PON1-162/-108/55/192 haplotype did not predict additional variation in PON1 activities compared with the 4 genotypes separately. PON1 hydrolysis activity predicted CAAD status, but this was not attributable to the promoter or coding region polymorphisms or haplotype or to the effects of smoking or statin use on PON1 activity.

*Conclusions*: PON1 does not have LD across the gene, and use of haplotypes in association studies should consider the LD structure. PON1 activity predicts CAAD, yet 4 functional polymorphisms do not. Additional investigations of genetic and environmental factors that influence PON1 activity as a risk factor for vascular disease are warranted.

*(Arterioscl Throm Vas 23:1465-1471, 2003)*
*ERIC Seattle, WA*

# CSP #97-010

# Continuous Improvement in Cardiac Surgery Program (CICSP)

This paper is part of the Department of Veterans Affairs (VA) Continuous Improvement in Cardiac Surgery Program (CICSP). The CICSP is a quality improvement program for coronary artery bypass graft surgery performed in 43 VA hospitals. A key part of the program is the study database, which is the foundation for comparative hospital reports as well as research reports.

## The Impact of Ethnicity on Outcomes Following Coronary Artery Bypass Graft Surgery in the Veterans Health Administration

RUMSFELD JS, PLOMONDON ME, PETERSON ED, SHLIPAK MG, MAYNARD C, GRUNWALD GK, GROVER FL, SHROYER ALW

**Abstract**: *Objectives*: We evaluated the effect of African American (AA) and Hispanic American (HA) ethnicity on mortality and complications following coronary artery bypass graft (CABG) surgery in the Veterans Health Administration (VHA).

*Background*: Few studies have examined the impact of ethnicity on outcomes following cardiovascular procedures.

*Methods*: This study included all 29,333 Caucasian, 2,570 AA, and 1,525 HA patients who underwent CABG surgery at any one of the 43 VHA cardiac surgery centers from January 1995 through March 2001. We evaluated the relationship between ethnicity (AA vs. Caucasian and HA vs. Caucasian) and 30-day mortality, 6-month mortality, and 30-day complications, adjusting for a wide array of demographic, cardiac, and noncardiac variables.

*Results*: After adjustment for baseline characteristics, AA and Caucasian patients had similar 30-day (AA/Caucasian odds ratio [OR] 1.07; 95% confidence interval [CI] 0.84 to 1.35; p = 0.59) and 6-month mortality risk (AA/Caucasian OR 1.10; 95% CI 0.91 to 1.34; p = 0.31). However, among patients with low surgical risk, AA ethnicity was associated with higher mortality (OR 1.52, CI 1.10 to 2.11, p = 0.01), and AA patients were more likely to experience complications following surgery (OR 1.28; 95% CI 1.14 to 1.45; p < 0.01). In contrast, HA patients had lower 30-day (HA/Caucasian OR 0.70; 95% CI 0.49 to 0.98; p = 0.04) and 6-month mortality risk (HA/Caucasian OR 0.66; 95% CI 0.50 to 0.88; p < 0.01) than Caucasian patients.

*Conclusions*: Ethnicity does not appear to be a strong risk factor for adverse outcomes following CABG surgery in the VHA. Future studies are needed to determine why AA patients have more complications, but ethnicity should not affect the decision to offer the operation.

*(J Am Coll Cardiol 40:1786-1793, 2002)*
*ERIC Seattle, WA*

# CSP #97-010

# Coronary Artery Bypass Surgeries (CABS) and Percutaneous Coronary Interventions (PCI)

This study compared the number of revascularization procedures and rates of use in the VA, the National Hospital Discharge Survey, and the Nationwide Inpatient Sample.

## Changes in the Use of Coronary Artery Revascularization Procedures in the Department of Veterans Affairs, the National Hospital Discharge Survey, and the Nationwide Inpatient Sample, 1991–1999

MAYNARD C, SALES AE

**Abstract:** *Background*: There have been dramatic increases in the number of coronary artery bypass surgeries (CABS) and percutaneous coronary interventions (PCI) performed during the last decade. Whether this finding is true for revascularization procedures performed in Department of Veterans Affairs (VA) medical centers is the subject of this paper.

*Methods*: This study compared the number of revascularization procedures and rates of use in the VA, the National Hospital Discharge Survey, and the Nationwide Inpatient Sample. Included were men who underwent isolated CABS and/or PCI, including stenting, between 1991 and 1999, although data for the Nationwide Inpatient Sample were available only between 1993 and 1997. Age adjusted use rates were calculated with the direct method of standardization.

*Results*: The percent of users of VA healthcare 75 years and older increased from 10% in 1991 to 20% in 1999. In the VA, the number of isolated CABS declined from 6227 in 1991 to 6147 in 1999, whereas age adjusted rates declined from 167.6 per 100,000 in 1991 to 107.9 per 100,000 in 1999. In the 2 national surveys, both the estimated numbers of procedures and use rates increased over time. In all 3 settings, there were increases in both numbers and rate of PCI from 1993, although in the VA, use rates decreased from 191.2 per 100,000 in 1996 to 139.7 per 100,000 in 1999. VA use rates for both CABS and PCI were lower than those in the 2 national surveys.

*Conclusion*: Age adjusted rates of CABS and PCI were lower in the VA than in 2 national surveys. Since 1996, there has been a decrease in the rate of use of revascularization procedures in the VA.

*(BMC Health Serv Res 3:12, 2003)*
*ERIC Seattle, WA*

# CSP #97-010

# Clinical Outcomes Assessment Program (COAP)

Begun in 1997, the Clinical Outcomes Assessment Program (COAP) of the state of Washington is an effort by the Washington State Health Care Authority in collaboration with the medical community to improve quality of care in the use of procedures relating to cardiovascular disease, specifically coronary artery bypass graft surgery and percutaneous coronary interventions. Since its inception, COAP has developed a comprehensive database that includes all of the cardiac revascularization procedures performed in the state. The database is the foundation for comparative reports that examine hospital performance as well as research studies that address key issues related to cardiac revascularization procedures.

Off-pump coronary artery bypass graft (CABG) surgery does not use the cardiopulmonary blood oxygenator pump to circulate blood while the patient is undergoing surgery to bypass occluded coronary arteries that restrict blood flow to the heart. Since the patient's heart is not stopped and since blood is not circulated outside the patient's body, there may fewer complications. Improving technology has lead to widespread use of off-pump surgery.

## Use of Off-Pump and On-Pump CABG Strategies in Current Clinical Practice: The Clinical Outcomes Assessment Program of the State of Washington

ALDEA GS, GOSS JR, BOYLE JR. EM, QUINTON RR, MAYNARD C

**Abstract:** *Background*: The purpose of this study is to assess clinical outcomes and regional differences in the use of on-pump and off-pump CABG in current clinical practice.

*Methods*: Between January 1, 1999, and December 31, 2000, there were 10,429 CABG procedures performed in 16 Washington state hospitals, all of which participate in Clinical Outcomes Assessment Program database. This analysis excluded patients with a history of prior CABG as well as those who underwent emergent surgery. After applying these exclusion criteria, 8402 patients (7169 on-pump and 1233 off-pump CABG procedures) were evaluated and presented as both unadjusted and risk-adjusted outcomes.

*Outcomes*: Off-pump CABG constituted 14.7% of all surgical revascularization procedures. These varied enormously among individual centers from an incidence of 0% to 68.9%. The use of off-pump CABG was not associated with a decreased risk of risk-adjusted hospital mortality or stroke, but was associated with a reduction in hospital stay > 7 days (OR 0.62, CI 0.51-0.76), ventilator > 24 hours (OR 0.52, CI 0.34-0.81), dialysis (OR 0.34, CI 0.14-0.86), and RBC transfusion (OR 0.5, CI 0.40-0.61).

*Conclusions*: Despite its highly variable use, off-pump CABG seems to be judiciously used in current clinical practice in the State of Washington and is associated with a decrease in morbidity in appropriately selected patients.

*(J Cardiac Surg 18:206-215, 2003)*
*ERIC Seattle, WA*

Begun in 1997, the Clinical Outcomes Assessment Program (COAP) of the state of Washington is an effort by the Washington State Health Care Authority in collaboration with the medical community to improve quality of care in the use of procedures relating to cardiovascular disease, specifically coronary artery bypass graft surgery and percutaneous coronary interventions. Since its inception, COAP has developed a comprehensive database that includes all of the cardiac revascularization procedures performed in the state. The database is the foundation for comparative reports that examine hospital performance as well as research studies that address key issues related to cardiac revascularization procedures.

The use of the left internal mammary artery (LIMA) in coronary artery bypass graft (CABG) surgery has been associated with improved long-term outcomes in patients who undergo this procedure.

## The Effect of Left Internal Mammary Artery Utilization on Short-Term Outcomes after Coronary Revascularization

DABAL RJ, GOSS JR, MAYNARD C, ALDEA GS

**Abstract**: *Background*: The purpose of this study was to determine whether use of the left internal mammary artery (LIMA) during coronary revascularization influences short-term morbidity in all patients undergoing revascularization, as well as in patients over the age of 75 years, female patients, and patients with diabetes. The study also explored variability in the utilization of LIMA grafts across an entire state.

*Methods*: Using the Clinical Outcomes Assessment Program (COAP) of the state of Washington, procedural outcomes were compared for patients receiving and patients not receiving LIMA grafts as part of revascularization procedures from January 1, 1999 to December 31, 2000. Mortality and major complications were examined, both as unadjusted rates and after adjusting for baseline patient risk factors.

*Results*: A total of 16 centers performed 8,797 nonemergent coronary artery revascularizations, including 81.7% with LIMA grafts. The use of a LIMA graft was associated with a significantly lower mortality (3.7% No LIMA vs. 1.6% LIMA), as well as decreases in ventricular arrhythmias, need for postoperative dialysis, need for transfusions, ventilator dependence, and length of hospital stay. These trends were true for the population as a whole as well as for all subgroups analyzed, and they persisted after correcting for differences in comorbid conditions. In addition, there was wide variability in the use of LIMA grafts from center to center in the state.

*Conclusions*: The use of LIMA grafts for coronary revascularization is associated with decreased mortality and morbidity. Despite these advantages, there is great variability in its application across the state of Washington.

*(Ann Thorac Surg 76:464-470, 2003)*
*ERIC Seattle, WA*

# Adjusting for Patient Differences in Predicting Hospital Mortality for Percutaneous Coronary Interventions in the Clinical Outcomes Assessment Program

MAYNARD C, GOSS JR, MALENKA DJ, REISMAN M

**Abstract:** *Background*: The Clinical Outcomes Assessment Program (COAP) is a coordinated quality improvement program for percutaneous coronary interventions (PCIs) performed in Washington State hospitals. This study describes the development and testing of models for predicting hospital mortality in patients undergoing PCI.

*Methods*: The COAP PCI database contains extensive demographic, medical history, and procedural information. This study included 19,358 consecutive PCIs performed in 27 Washington hospitals in 1999 and 2000. The study population was randomly assigned to development (n = 11,591) and test (n = 7614) sets. Logistic regression mortality models were run in the development set and evaluated in the test set.

*Results*: The test and development sets were similar in demographic, medical history, and procedural characteristics. The overall hospital mortality rate was 1.6% and was similar in the test and development sets. By means of stepwise logistic regression analysis, cardiogenic shock, age, nonelective priority, elevated creatinine level, ejection fraction, number of diseased vessels, myocardial infarction <24 hours from admission, history of chronic obstructive pulmonary disease, male sex, history of peripheral vascular disease, history of PCI, and history of congestive heart failure were identified as predictors of hospital mortality. When applied to the test set, this model had excellent discrimination (c statistic = 0.87, 95% CI = 0.84-0.90). The model was also evaluated in the Northern New England PCI Registry, with very good results (c statistic = 0.85).

*Conclusion*: Developing risk-adjusted models of mortality and other outcomes is an essential part of the quality improvement process for cardiac revascularization procedures. Because of the rapidly changing nature of PCI, modification of these models in the years to come will be required.

*(Am Heart J 145:658-664, 2003)*
*ERIC Seattle, WA*

# CSP #465

# Glycemic Control and Complications in Diabetes Mellitus Type II

Diabetes can have many serious complications, including increased risk for heart disease, eye problems, problems with the circulatory system and nervous system, and kidney disease. Previous research has demonstrated that strict glycemic control can prevent the microvascular complications of the disease, but this has not been proven for the macrovascular complications. CSP #465 has randomized 1792 patients at 20 VA medical centers to a regimen of strict glycemic control vs. standard control. Patients will be followed until 2007. The primary outcome variable is cardiovascular morbidity and mortality.

The article below describes the study design.

## Design of the Cooperative Study on Glycemic Control and Complications in Diabetes Mellitus Type 2 Veterans Affairs Diabetes Trial

CARLOS ABRAIRA, WILLIAM DUCKWORTH, MADELINE MCCARREN, NICHOLAS EMANUELE, DANIELLE ARCA, DOMENIC REDA, WILLIAM HENDERSON FOR THE PARTICIPANTS OF THE VA COOPERATIVE STUDY OF GLYCEMIC CONTROL AND COMPLICATIONS IN DIABETES MELLITUS TYPE 2

**Abstract:** *Introduction:* Long-term glycemic control trials in type 2 diabetes show as the main clinical benefit a difference in retinal photocoagulation, but no effect on visual acuity or renal failure. No intensive glycemic control trial has yet affected cardiovascular (CV) events, the main cause of morbidity and mortality. By contrast, modest blood pressure reduction has protective effects on visual acuity, renal function, CV events, and mortality. Optimal glycemic control goals are not established in elderly, obese persons with advanced complications, the most common patients in the VA system. The earlier feasibility trial in such patients (VA-CSDM) suggested potentially worse CV outcomes with lower attained hemoglobin Alc (HbAlc) levels.

*Objectives:* The primary objective of the Veterans Affairs Diabetes Trial (VADT) is the assessment of the effect of intensive glycemic treatment on CV events. Other objectives are effects on microangiopathy, quality of life, and cost effectiveness.

*Research Design & Methods:* The VADT, started in December 2000, is enrolling 1700 men and women previously uncontrolled on insulin or maximum doses of oral agents at 20 VA medical centers. Accrual is 2 years and follow-up is 5-7 years, with visits every 1.5 months. The study has a power of 86% to detect a 21% relative reduction in major CV events. Subjects are randomized to an intensive arm aiming at normal HbAlc levels or to a standard

arm with usual, improved glycemic control. An HbAlc separation of >1.5% is to be maintained (expected 2%). Both arms receive step therapy: glimepiride or metformin plus rosiglitazone and addition of insulin or other oral agents to achieve goals. Strict control of blood pressure and dyslipidemia, daily aspirin, diet, and education are identical in both arms. Plasma fibrinogen, plasminogen-activating inhibitor, lipids, renal function parameters, and ECG are measured throughout. Stereo retinal photographs are obtained at entry and 5 years, eye examinations yearly, and intervention as needed to prevent visual deterioration. Recruitment is proceeding on schedule.

*(J Diabetes and Its Complications 17:314-322, 2003)*
*CSPCC Hines, IL*

# CSP #705D

# Screening for Diabetes Mellitus in Veterans

The Screening for Diabetes Mellitus (DM) in Veterans study was a cross-sectional observational study of veterans with diabetes. The primary objective of the study was to measure the prevalence of undiagnosed diabetes mellitus and the annual incidence of new cases of DM among veterans between the ages of 45 and 64 and to compare the health-related quality of life (HRQOL) of veterans with undiagnosed DM to those without DM but who are at comparable risk for DM, both at baseline and over three years of follow-up.

The articles described below present results from the study regarding quality of care for patients diagnosed with diabetes at screening, and the relationship between obesity and health-related quality of life in men.

## Relationship between Obesity and Health-Related Quality of Life in Men

WILLIAM YANCY, JR, MD, MAREN OLSEN, PHD, ERIC WESTMAN, MD, HAYDEN BOSWORTH, PHD, DAVID EDELMAN, MD, MHS

**Abstract:** Few studies examining the relationship between obesity and health-related quality of life (HRQOL) have used a medical outpatient population or demonstrated a relationship in men. Furthermore, most studies have not adequately considered comorbid illness. The goal of this study was to examine the relationship between body mass index (BMI) and HRQOL in male outpatients while considering comorbid illness.

This cross-sectional study examined 1,168 male outpatients from the Durham Veterans Affairs Medical Center. Multiple linear regression was used to examine the relationship of BMI with each subscale from the Medical Outcomes Study Short Form 36 while adjusting for age, race, comorbid illness, depression, and physical activity.

An inverse relationship between BMI and physical aspects of HRQOL exists in a population of male outpatients. Increased BMI was most prominently associated with bodily pain; this relationship should receive more attention in clinical care and research.

*(Obesity Research 10:1057-1064, 2002)*
*ERIC Durham, NC*

# Quality of Care for Patients Diagnosed With Diabetes at Screening

DAVID EDELMAN, MD, MHS, MAREN OLSEN, PHD, TARA DUDLEY, MSTAT, AMY HARRIS, BA, EUGENE ODDONE, MD, MHS

**Abstract:** Screening for diabetes has the potential to be an effective intervention, especially if patients have intensive treatment of their newly diagnosed diabetes and comorbid hypertension. This study examines the process and quality of diabetes care for patients diagnosed with diabetes by systematic screening.

A total of 1,253 users of the Durham Veterans Medical Center aged 45-64 years who did not report having diabetes were screened for diabetes with an $HbA_{1c}$ test. All subjects with an $HbA_{1c}$ level $\geq$ 6.0% were invited for follow-up blood pressure and fasting plasma glucose (FPG) measurements. A case of unrecognized diabetes was defined as $HbA_{1c} \geq 7.0\%$ or FPG > 126 mg.dl. For each of the 56 patients for whom we made a new diagnosis of diabetes, we notified the patient's primary care provider of this diagnosis. One year after diagnosis, we reviewed these patients' medical records for traditional diabetes performance measures as well as blood pressure. Follow-up blood pressure was also ascertained from medical record review for all subjects with $HbA_{1c} \geq 6.0\%$ who did not have diabetes. We compared blood pressure changes between patients with and without diabetes.

Among patients diagnosed with diabetes at screening, 34 of 53 (64%) had evidence of diet or medical treatment for their diabetes, 42 of 53 (79%) had $HbA_{1c}$ measured within the year after diagnosis, 32 of 53 (60%) had cholesterol measured, 25 of 53 (47%) received foot examinations, 29 of 53 (55%) had eye examinations performed by an eye specialist, and 16 of 53 (30%) had any measure of urine protein. The mean blood pressure decline over the year after diagnosis for patients with diabetes was 2.3 mmHg; this decline was similar to that found for 183 patients in the study without diabetes (change in blood pressure, -3.6 mmHg). At baseline, 48% of patients with diabetes had blood pressure < 140/90, compared with 40% of patients without diabetes; 1 year later, the same 48% of patients with diabetes had blood pressure < 140/90, compared with 56% of patients without diabetes ($P$ = 0.31 for comparing the change in percent in control between groups).

Patients with diabetes diagnosed at screening achieve less tight blood pressure control than similar patients without diabetes. Primary care providers do not appear to manage diabetes diagnosed at screening as intensively as long-standing diabetes and do not improve the management of hypertension given the new diagnosis of diabetes.

*(Diabetes Care 26:367-371, 2003)*
*ERIC Durham, NC*

# CSP #97-010

# Behavioral Risk Factor Surveillance System (BRFSS)

A national telephone survey called the Behavioral Risk Factor Surveillance System (BRFSS) is conducted every year in the United States and its territories. For the first time in 2001, the BRFSS classified Asian Americans as a distinct group. This is important, because little is known about the health of Asian Americans. We used the information from the 2001 BRFSS to see if Asian Americans are more likely to have diabetes than whites. We found that after accounting for differences in age, sex, and obesity, Asian Americans were 60% more likely to have diabetes than whites.

Similar proportions of Asian Americans and whites report having diabetes. However, after taking into account the fact that Asians are less likely to be overweight or obese, the proportion of Asian Americans with diabetes was 60% higher than in whites.

## Type 2 Diabetes Prevalence in Asian Americans: Results of a National Health Survey

MCNEELY MJ, BOYKO EJ

**Abstract:** *Objective*: Asians are thought to be at high risk for diabetes, yet there is little population-based information about diabetes in Asian Americans. The purpose of this study was to directly compare the prevalence of type 2 diabetes in Asian Americans with other racial and ethnic groups in the U.S. using data from the 2001 Behavioral Risk Factor Surveillance System (BRFSS).

*Research Design and Methods:* The BRFSS is a population-based telephone survey of the health status and health behaviors of Americans in all 50 states, Guam, Puerto Rico, and the U.S. Virgin Islands. Subjects included 3,071 Asians, 12,561 blacks, 12,153 Hispanics, 2,299 Native Americans, 626 Pacific Islanders, and 129,116 non-Hispanic whites aged >/=30 years. Subjects who reported a physician-diagnosis of diabetes were considered to have type 2 diabetes unless they were diagnosed before age 30.

*Results:* Compared with whites, odds ratios (95% CIs) for diabetes, adjusted for age and sex, were 1.0 (0.7-1.4) for Asians, 2.3 (2.1-2.6) for blacks, 2.0 (1.8-2.3) for Hispanics, 2.2 (1.6-2.9) for Native Americans, and 3.1 (1.4-6.8) for Pacific Islanders. Results adjusted for BMI, age, and sex were 1.6 (1.2-2.3) for Asians, 1.9 (1.7-2.2) for blacks, 1.9 (1.6-2.1) for Hispanics, 1.8 (1.3-2.5) for Native Americans, and 3.0 (1.4-6.7) for Pacific Islanders.

*Conclusions:* Similar proportions of Asian and non-Hispanic white Americans report having diabetes, but after accounting for the lower BMI of Asians, the adjusted prevalence of diabetes is 60% higher in Asian Americans.

*(Diabetes Care 27:66-69, 2004)*
*ERIC Seattle, WA*

# CSP #1008

## Buprenorphine/Naloxone for Treatment of Opiate Dependence

The cost-effectiveness of buprenorphine treatment for opiate dependence is estimated using a mathematical detail of a model that considers effects on the HIV epidemic, mortality, and health care costs. The study determined that buprenorphine will be cost-effective if it is sold for $5 per dose. If it is sold for $15 per dose, it will be cost-effective only if its adoption does not lead to a new decline in methadone use, or if a medium to high value is assigned to the years of life lived by injection drug users and those in maintenance therapy. Buprenorphine adoption will result in significant health benefits to the general population by reducing the spread of HIV.

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## Office-Based Treatment of Opiate Addiction with Sublingual-Tablet Formulation of Buprenorphine and Naloxone

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**Abstract:** *Background*: Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone has been proposed, but its efficacy and safety have not been well studied.

*Methods*: We conducted a multicenter, randomized, placebo-controlled trial involving 326 opiate-addicted persons who were assigned to office-based treatment with sublingual tablets consisting of buprenorphine (16 mg) in combination with naloxone (4 mg), buprenorphine along (16 mg), or placebo given daily for four weeks. The primary outcome measures were the percentage of urine samples negative for opiates and the subjects' self-reported craving for opiates. Safety data were obtained on 461 opiate-addicted persons who participated in an open-label study of buprenorphine and naloxone (at daily doses of up to 24 mg and 6 mg, respectively) and another 11 persons who received this combination only during the trial.

*Results*: The double-blind trial was terminated early because buprenorphine and naloxone in combination and buprenorphine alone were found to have greater efficacy than placebo. The proportion of urine samples that were negative for opiates was greater in the combined-treatment and buprenorphine groups (17.8 percent and 20.7 percent, respectively) than in the placebo group (5.8 percent, $P<0.001$ for both comparisons); the active-treatment groups also reported less opiate craving ($P<0.001$ for both

comparisons with placebo). Rates of adverse events were similar in the active-treatment and placebo groups. During the open-label phase, the percentage of urine samples negative for opiates ranged from 35.2 percent to 67.4 percent. Results from the open-label follow-up study indicated that the combined treatment was safe and well tolerated.

*Conclusions*: Buprenorphine and naloxone in combination and buprenorphine alone are safe and reduce the use of opiates and the craving for opiates among opiate-addicted persons who receive these medications in an office-based setting.

*(NEJM 349:949-958, 2003)*
*CSP CRPCC Albuquerque, NM and CSPCC Perry Point, MD*

# CSP #265

# Treatment of Generalized Convulsive Status Epilepticus

Data and Safety Monitoring Boards (DSMB) are charged with reviewing studies on an ongoing basis to ensure that the study is progressing satisfactorily and that patient safety is not being compromised. The VA's Status Epilepticus Cooperative Study was a randomized, multicenter clinical trial testing four intravenous drug regimens (lorazepam, phenobarbital, phenytoin, and diazepam followed by phenytoin) for the treatment of generalized convulsive status epilepticus, a life threatening, neurologic emergency that must be stopped quickly to prevent severe, permanent brain damage or death. In this study, there were two major problems that the study's DSMB had to address with the study leadership: poor recruitment and an unexpected difference between treatment groups in 30-day death rates that was seen at the beginning of the study. For the poor recruitment problem, the DSMB recommended approval of proposed changes in the study design, of a two year increase of recruitment period and a decrease of required sample size contingent on study leadership terminating nonproductive sites. Concerning the unexpected 30-day mortality, the DSMB demanded monthly reporting to them on mortality and suggested analyses for exploring why the differences were occurring. These analyses indicated that, by chance, older and sicker patients had been randomized to the drugs with the higher death rates. By the end of the study, the differences in mortality had disappeared. Due to the DSMB working with the study leadership and carefully monitoring study progress, the study was successfully completed without endangering the study patients.

## Data and Safety Monitoring Board Issues Raised in the VA Status Epilepticus Study

JOSEPH F. COLLINS, SCD

**Abstract:** The Department of Veterans Affairs Status Epilepticus Cooperative Study was a randomized, multicenter clinical trial testing four intravenous drug regimens (lorazepam, phenobarbital, phenytoin and diazepam followed by phenytoin) to treat generalized convulsive status epilepticus. During the course of the study, two problems emerged that the study's Data and Safety Monitoring Board (DSMB) was required to address: poor recruitment and an unexpected difference in 30-day mortality between treatment groups. By the first annual DSMB meeting, recruitment was only 25.6% of expected. The DSMB recommended placing the study on probation and replacing poorly performing sites. At their second annual meeting, the DSMB recommended approval of proposed changes to the study design contingent on the study leadership removing nonproductive

sites. These changes were a 2-year increase in the recruitment period and a change in study design that decreased required sample size. Nonproductive centers were terminated, and the approved changes allowed the study to be successfully completed. At the second annual DSMB meeting, an unexpected doubling of mortality rates between drug groups was observed. Although not statistically significant, the finding raised serious concerns for patient safety. The DSMB recommended instituting monthly reporting on mortality and suggested additional analyses for exploring why the differences could be occurring. These analyses indicated that, by chance, older and sicker patients were being randomized to the drugs with the higher mortality rates. By the end of the study, the observed differences in mortality between drug groups had evened out. The DSMB's thoughtful recommendations, support and monitoring ensured that the study was successfully completed without endangering the study patients.

*(Control Clin Trials 24:71-77, 2003)*
*CSPCC Perry Point, MD*

# CSP #006

# Evaluation of GEM Units and Geriatric Follow-up

The overall goal of this Cooperative Study is to evaluate the effectiveness of inpatient GEM Units (GEMU) and post-hospital follow-up care in GEM clinics (GEMC). We conducted a randomized trial involving frail patients 65 years of age or older who were hospitalized at 11 Veterans Affairs medical centers. After their condition had been stabilized, patients were randomly assigned, according to a two-by-two factorial design, to receive either care in an inpatient geriatric unit or usual inpatient care, followed by either care at an outpatient geriatric clinic or usual outpatient care.

In this controlled trial, care provided in inpatient geriatric units and outpatient geriatric clinics had no significant effects on survival. There were significant reductions in functional decline with inpatient geriatric evaluation and management and improvements in mental health with outpatient geriatric evaluation and management, with no increase in costs.

## A Controlled Trial of Inpatient and Outpatient Geriatric Evaluation and Management

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DONALD COURTNEY, MD, KENNETH W. LYLES, MD, CONRAD MAY, MD, CYNTHIA MC MURTY, MD,
LESLYE PENNYPCKER, MD, DAVID M. SMITH, MD, NINA AINSLIE, MD, THOMAS HORNICK, MD,
KAYLA BRODKIN, MD, AND PHILIP LAVORI, PH D

**Abstract:** *Background:* Over the past 20 years, both inpatient units and outpatient clinics have developed programs for geriatric evaluation and management. However, the effects of these interventions on survival and functional status remain uncertain.

*Methods:* We conducted a randomized trial involving frail patients 65 years of age or older who were hospitalized at 11 Veterans Affairs medical centers. After their condition had been stabilized, patients were randomly assigned, according to a two-by-two factorial design, to receive either care in an inpatient geriatric unit or usual inpatient care, followed by either care at an outpatient geriatric clinic or usual outpatient care. The interventions involved teams that provided geriatric assessment and management according to Veterans Affairs standards and published guidelines. The primary outcomes were survival and health-related quality of life, measured with the use of the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36), one year after randomization. Secondary outcomes were the ability to perform activities of daily living, physical performance, utilization of health services, and costs.

*Results:* A total of 1388 patients were enrolled and followed. Neither the inpatient nor the outpatient intervention had a significant effect on mortality (21 percent at one year overall), nor were there any synergistic effects between the two interventions. At discharge, patients assigned to the inpatient geriatric units had significantly greater improvements in the scores for four of the eight SF-36 subscales, activities of daily living, and physical performance than did those assigned to usual inpatient care. At one year, patients assigned to the outpatient geriatric clinics had better scores on the SF-36 mental health subscale, even after adjustment for the score at discharge, than those assigned to usual outpatient care. Total costs at one year were similar for the intervention and usual-care groups.

*Conclusions:* In this controlled trial, care provided in inpatient geriatric units and outpatient geriatric clinics had no significant effects on survival. There were significant reductions in functional decline with inpatient geriatric evaluation and management and improvements in mental health with outpatient geriatric evaluation and management, with no increase in costs.

*(N Engl J Med 346:905-912, 2002)*
*CSPCC Palo Alto, CA*

# CSP #470

# A Randomized, Multi-center, Controlled Trial of Multi-Modal Therapy in Gulf War Illnesses

CSP #470 was a randomized trial designed to evaluate the effectiveness of aerobic exercise and cognitive behavioral therapy (CBT) in 1092 veterans with Gulf War Veterans' Illnesses (GWVI). Veterans were treated for three months and followed for twelve months. The results suggested that CBT and/or exercise could provide modest relief of symptoms.

Overall, the study found that CBT improved physical function whereas exercise relieved many of the symptoms of GWVI related to fatigue and distress; both therapies improved cognitive symptoms and mental health functioning but neither therapy improved pain.

## Cognitive Behavioral Therapy and Aerobic Exercise for Gulf War Veterans' Illnesses
## A Randomized Controlled Trial

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**Abstract***: Context:* Gulf War veterans' illnesses (GWVI), multisymptom illnesses characterized by persistent pain, fatigue, and cognitive symptoms, have been reported by many Gulf War veterans. There are currently no effective therapies available to treat GWVI.

*Objective:* To compare the effectiveness of cognitive behavioral therapy (CBT), exercise, and the combination of both for improving physical functioning and reducing the symptoms of GWVI.

*Design, Setting, and Patients:* Randomized controlled 2x2 factorial trial conducted from April 1999 to September 2001 among 1092 Gulf War veterans who reported at least 2 of 3 symptom types (fatigue, pain, and cognitive) for more than 6 months and at the time of screening. Treatment assignment was unmasked except for a masked assessor of study outcomes at each clinical site (18 Department of Veterans Affairs [VA] and 2 Department of Defense [DOD] medical centers)

*Interventions:* Veterans were randomly assigned to receive usual care (n=271), consisting of any and all care received from inside or outside the VA

or DOD health care systems; CBT plus usual care (n=286); exercise plus usual care (n=269); or CBT plus exercise plus usual care (n=266). Exercise sessions were 60 minutes, and CBT sessions were 60 to 90 minutes; both met weekly for 12 weeks.

*Main Outcome Measures:* The primary end point was a 7-point or greater increase (improvement) on the Physical Component Summary scale of the Veterans Short Form 36-Item Health Survey at 12 months. Secondary outcomes were standardized measures of pain, fatigue, cognitive symptoms, distress, and mental health functioning. Participants were evaluated at baseline and at 3, 6, and 12 months.

*Results:* The percentage of veterans with improvement in physical function at 1 year was 11.5% for usual care, 11.7% for exercise alone, 18.4% for CBT plus exercise, and 18.5% for CBT alone. The adjusted odds ratios (OR) for improvement in exercise, CBT, and exercise plus CBT vs usual care were 1.07 (95% confidence interval [CI], 0.63-1.82), 1.72 (95% CI, 0.91-3.23), and 1.84 (95% CI, 0.95-3.55), respectively. The OR for the overall (marginal) effect of receiving CBT (n=552) vs no CBT (n=535) was 1.71 (95% CI, 1.15-2.53) and for exercise (n=531) vs no exercise (n=556) was 1.07 (95% CI, 0.76-1.50). For secondary outcomes, exercise alone or in combination with CBT significantly improved fatigue, distress, cognitive symptoms, and mental health functioning, while CBT alone significantly improved cognitive symptoms and mental health functioning. Neither treatment had a significant impact on pain.

*Conclusion:* Our results suggest that CBT and/or exercise can provide modest relief for some of the symptoms of chronic multisymptom illnesses such as GWVI.

*(JAMA 289 (11):1396-1404, 2003)*
*CSPCC West Haven, CT*

# CSP #500

# A Study of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans

In response to Gulf War veterans' concerns of high rates of ALS, this investigation sought to determine if veterans have an elevated rate of ALS. In response to this concern, a nationwide epidemiologic case ascertainment study design was used to ascertain all occurrences of ALS for the 10-year period since August 1990 among active duty military and mobilized Reserves, including National Guard, who served during the Gulf War. VA led this joint federal government epidemiologic study that also involved DoD, HHS, CDC, and academic centers of excellence in neurology, with advice from the ALS Association.

The article described below presents results from the study regarding the occurrence of ALS among deployed Gulf War veterans as compared to non-deployed Gulf War veterans.

## Occurrence of Amyotrophic Lateral Sclerosis Among Gulf War Veterans

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**Abstract:** A nationwide epidemiologic case ascertainment study design was used to ascertain all occurrences of ALS for the 10-year period since August 1990 among active duty military and mobilized Reserves, including national Guard, who served during the Gulf War (August 2, 1990 through July 31, 1991). The diagnosis of ALS was confirmed by medical record review. Risk was assessed by the age-adjusted, average, annual 10-year cumulative incidence rate.

Among approximately 2.5 million eligible military personnel, 107 confirmed cases of ALS were identified for an overall occurrence of 0.43 per 100,000 persons per year. A significant elevated risk of ALS occurred among all deployed personnel. Elevated, but non-significant risks were observed for deployed Reserves and National Guard, deployed Navy, and deployed Marine Corps personnel. Overall, the attributable risk associated with deployment was 18%.

Military personnel who were deployed to the Gulf Region during the Gulf War period experienced a greater post-war risk of ALS than those who were deployed to the Gulf.

*(Neurology 61:730-731, 2003)*
*ERIC Durham, NC*

# CSP #418

## NIDCD/VA Hearing Aid Trial

It is estimated that 25 million Americans have a hearing impairment. It is further estimated that 14 million of them could benefit from a hearing aid. The Department of Veterans Affairs fits 60,000 veterans with hearing aids each year. Given these numbers, there is a surprising lack of information regarding which types of hearing aids perform best. This trial examined subjects with binaural sensorineural hearing loss in order to compare the safety and efficacy of three commonly used hearing aid circuits; linear amplification with peak clipping, linear amplification with compression limiting, and wide dynamic range compression. This trial also determined if there are certain circuits that are particularly suited to certain types of subjects.

Article #1: Discusses the results of the PHAP and a simple subjective rating of these circuits.

Article #2: Reports details of a large-scale study of benefit provided by three conventional hearing aid circuits that command a significant portion of the "market share."

Article #3: Presents the results of the rigorous control of the electroacoustic characteristics of the experimental devices.

Article #4: This article describes the organization and administration of the NIDCD/VA Hearing Aid Clinical Trial.

Article #5: Describes the quality rating test (QRT) for three listening dimensions: loudness, noise interference, and overall liking or impression.

Article #6: Focuses on two measures of speech recognition chosen as criterion measures of hearing aid benefit.

# Subjective Measures of Hearing Aid Benefit in the NIDCD/VA Clinical Trial

GEORGE B. HASKELL, DOUGLAS NOFFSINGER, VERNON D. LARSON, DAVID W. WILLIAMS, ROBERT A. DOBIE, JANETTE L. ROGERS

**Abstract:** *Objective:* Subjective measures of performance were assessed on three different hearing aid circuits as part of a large clinical trial. These measurements included the Profile of Hearing Aid Performance and a subjective ranking of individual preference.

*Design:* A multi-center, double-masked clinical trial of hearing aids was conducted at eight VA medical centers. Three hearing aid circuits, a linear peak-clipper, a linear compression limiter, and a wide dynamic range compressor, were investigated. The experimental design was a three-period, three-treatment crossover design. Subjects (*N*=360) were stratified by site and randomized to one of six sequences for the hearing aid circuits. All fittings were binaural and involved a 3-mo trial with each of the three circuits. All subjective measures were administered for unaided and aided conditions at the end of each trial period.

*Results:* While all of the circuits resulted in improved scores on the aided versus the unaided PHAP, there were few conditions in which one circuit outperformed the others. An exception was the aversiveness of sound subscale where the peak clipper frequently scored worse than either the compression limiter or the wide dynamic range compressor. In the subjective ranking scale the compression limiter received more first place rankings than the other two circuits, especially for one subgroup of patients with moderate flat hearing loss.

*Conclusions:* All circuits were perceived as beneficial by these subjects in most situations. The peak clipper scored worse on aversiveness of sound than did the other two circuits for most subjects, while the compression limiter seemed to have a slight advantage in subjective rankings. Most subjects perceived considerable aided benefit in situations involving background noise and reverberation, situations where hearing aid benefit is often questioned.

*(Ear & Hearing 23:301-307,2002)*
*CSPCC Hines, IL*

# A Multi-Center, Double Blind Clinical Trial Comparing Benefit from Three Commonly Used Hearing Aid Circuits

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**Abstract:** *Objectives:* Although numerous studies have demonstrated that hearing aids provide significant benefit, carefully controlled, multi-center clinical trials have not been conducted. A multi-center clinical trial was conducted to compare the efficacy of three commonly used hearing aid circuits: peak clipping, compression limiting, and wide dynamic range compression.

*Design:* Patients (*N*=360) with bilateral, sensorineural hearing loss were studied using a double blind, three-period, three-treatment crossover design. The patients were fit with each of three programmable hearing aid circuits. Outcome tests were administered in the unaided condition at baseline and then after 3 mo usage of each circuit, the tests were administered in both aided and unaided conditions. The outcome test battery included tests of speech recognition, sound quality and subjective scales of hearing aid benefit, including patients' overall rank-order rating of the three circuits.

*Results:* Each hearing aid circuit improved speech recognition markedly, with greater improvement observed for soft and conversationally loud speech in both quiet and noisy listening conditions. In addition, a significant reduction in the problems encountered in communication was observed. Some tests suggested that the two compression hearing aids provided a better listening experience than the peak clipping hearing aid. In the rank-order ratings, patients preferred the compression limiting hearing aid more frequently than the other two hearing aids.

*Conclusions:* The three hearing aid circuits studied provide significant benefit both in quiet and in noisy listening situations. The two compression hearing aids appear to provide superior benefits compared to the linear circuit, although the differences between the hearing aids were smaller than the differences between unaided and aided conditions.

*(Ear & Hearing 23:269-276, 2002)*
*CSPCC Hines, IL*

## Coupler and Real-Ear Measurement of Hearing Aid Gain and Output in the NIDCD/VA Hearing Aid Clinical Trial

GENE W. BRATT, MIA A.L. ROSENFELD, BARBARA F. PEEK, JOYCE KANG, DAVID W. WILLIAMS, VERNON LARSON

**Abstract:** *Objective:* Because the NIDCD/VA Hearing Aid Clinical Trial was conducted across eight clinical sites, rigorous control of the electroacoustic characteristics of the experimental devices was required.

*Design:* The parameters monitored included the gain and output of the approximately 720 hearing aids in the trial, measured both in the 2 $cm^3$ coupler and in situ. Each measurement was repeated six times on each hearing aid across the 9-mo duration of the study to insure both the stability and the accuracy of the circuits under investigation.

*Results:* The gain data obtained in the coupler and in situ adequately demonstrated the stability of the instrument and the repeated measurements over time and across study sites. The output values produced by the experimental device also maintained acceptable constancy, both within and across treatment periods.

*Conclusions:* These measurements reflected satisfactory stability and sufficient accuracy within the circuits to achieve the intended goals of the study.

*(Ear & Hearing 23:308-315, 2002)*
*CSPCC Hines, IL*

## Organization and Administration of the NIDCD/VA Hearing Aid Clinical Trial

WILLIAM G. HENDERSON, VERNON D. LARSON, DAVID WILLIAMS, AND LYNN LUETHKE

**Abstract:** This article describes the organization and administration of the NIDCD/VA Hearing Aid Clinical Trial. The trial involved a total of 360 patients with bilateral, sensorineural hearing loss from eight VA medical centers to study three different hearing aid circuits in a three-period, three-treatment crossover design. Strong central coordination of such a complex multi-center clinical trial is essential to its success. The trial took more than five years to design, implement, and complete. This time-line is also described.

*(Ear & Hearing 23:277-279, 2002)*
*CSPCC Hines, IL*

# Speech Recognition Performance of Patients with Sensorineural Hearing Loss Under Unaided and Aided Conditions Using Linear and Compression Hearing Aids

JANET E. SHANKS, RICHARD H. WILSON, VERN LARSON, AND DAVID WILLIAMS

**Abstract:** *Objectives:* This study compared speech recognition performance on the Northwestern University Auditory Test No. 6 (NU-6) and the Connected Speech Test (CST) for three hearing aid circuits (peak clipping [PC], compression limiting [CL], and wide dynamic range compression [WDRC]) in adults with symmetrical sensorineural hearing loss. The study also questioned whether or not hearing aid benefit for the three circuits was dependent upon the speech level and the signal-to-babble ratio (S/B) and upon the degree and slope of hearing loss.

*Design:* Unaided speech recognition performance for NU-6 and CST materials presented from a loud-speaker at $0^o$ was measured during Visit 1, and both unaided and aided performance was measured at 3-mo intervals during Visits 2 to 4. The NU-6 was presented in quiet at a conversational speech level of 62 dB SPL. The CST was presented in 10 listening conditions—three S/B (-3, 0, and 3 dB) at each of three speech levels (soft speech at 52 dB SPL, conversational speech at 62 dB SPL, and loud speech at 74 dB SPL) and in quiet at 74 dB SPL. Uncorrelated multi-talker babble was presented from two loud-speakers at $45^o$ on each side of the main speaker. Hearing aid benefit was examined for 360 subjects divided into four groups of hearing loss, pure tone average <40 dB HL and slope <10 dB/octave or >10 dB/octave and hearing loss >40 dB HL for the two slope categories.

*Results:* Hearing aid benefit (aided minus unaided performance) measured on the NU-6 in quiet exceeded 31 rau for all three circuits. Although small statistical advantages were found for the WDRC, the differences were ~2% and are not considered clinically relevant. Unaided CST performance showed a complex relationship between presentation level and signal-to-babble ratio that was further confounded by the degree of hearing loss. For the two mild hearing loss groups and for each of the three nominal signal-to-babble ratios, CST performance *decreased* by 20 rau for the –3 DB S/B to 6 rau for the 3 dB S/B as speech level *increased* from 52 to 74 dB SPL. In contrast, unaided performance *increased* by 32 to 13 rau with signal level for all signal-to-babble ratios for the two >40 dB hearing loss groups. Overall, aided CST performance exceeded unaided performance for all 10 conditions. As expected, hearing aid

benefit was greatest (27 rau) for soft speech and smallest for loud speech (6 rau). Differences among the hearing aid circuits were small with only one significant difference; the WDRC at 62/0 was poorer by 3 rau than the other two circuits. When the CST data were analyzed as a function of hearing loss, five pair-wise comparisons were significant. In contrast to the unaided performance, aided performance for all hearing loss groups decreased as presentation level increased, even though the signal-to-babble ratio was constant.

*Conclusions:* All three hearing aids circuits provided benefit over the unaided condition in both quiet and noise. The greatest benefit was measured for soft speech in the more severe hearing loss groups. Although only small differences were measured among the three hearing aid circuits, significant differences favored the PC and CL circuits over the WDRC in the mild hearing loss groups and favored the WDRC over the PC in the more severe, sloping hearing loss group. An interesting interaction between speech level, signal-to-babble ratio, degree of hearing loss, and amplification was found. For a constant signal-to-babble ratio, recognition performance decreased as speech level increased from 52 to 74 dB SPL. The effect was most marked in the milder hearing loss groups and in the aided conditions, and occurred at even the lowest speech levels.

*(Ear & Hearing 23:280-290, 2002)*
*CSPCC Hines, IL*

# Quality Rating Test of Hearing Aid Benefit in the NIDCD/VA Clinical Trial

DOUGLAS NOFFSINGER, GEORGE B. HASKELL, VERNON D. LARSON, DAVID W. WILLIAMS, ELEANOR WILSON, SHERIL PLUNKETT, DIANE KENWORTHY

**Abstract:** *Objective:* As part of a large clinical trial that compared three hearing aid circuits using several evaluation methods, judgments about quality of listening experiences were sought from all subjects. Three dimensions were examined: loudness, noise interference and overall liking (quality).

*Design:* Eight Audiology units in VA medical centers participated. Three hearing aid circuits were compared: linear peak clipper, compression limiter, and wide dynamic range compressor. The experimental design was a three-period, three-treatment crossover design. Baseline measures were made using a battery of tests in unaided conditions. Subjects (*N*=360) were then stratified by participating site and randomized to one of six sequences of the three hearing aid circuits. Each circuit was fit binaurally, and all subjects used each of the three circuits for 3 mo. All outcome measures were administered in unaided and aided conditions after each 3-mo period. The study used a double-blind strategy, i.e., neither the audiologist giving the tests nor the subject knew which circuit was being used. A different audiologist programmed the devices.

*Results:* For loudness judgments, soft and loud presentations of speech in quiet and in babble competition were judged more comfortable via the wide dynamic range circuit. The noise interference tasks and overall liking of the listening experience showed few significant differences across circuits. All circuits made the listening experience more comfortably loud for soft and conversation-level speech.

*Conclusions:* Differences across circuits in terms of the overall quality of the listening experience and how noise interference was rated were small. Only isolated conditions, usually favoring the WDRC circuit, reached significance levels. The loudness dimension results were clearer. The WDRC circuit made sounds at either the loud or soft extreme more comfortable. When subjects were grouped by amount and configuration of hearing loss, the advantages for the WDRC and to a lesser extent the linear compression-limited circuit were clearest among subjects with mild hearing losses with a >10 dB/octave high-frequency drop, and those with moderate, relatively flat hearing losses.

(*Ear & Hearing 23:291-300, 2002)*
*CSPCC Hines, IL*

# CSP #512

# Options in Management with Antiretrovirals (OPTIMA)

OPTIMA is a Tri-National collaboration among the VA, Canadian Institutes of Health Research and the U.K. Medical Research Council. The study is designed to find the best way to treat people who have taken a wide range of anti-HIV drugs in several different combinations and who now have a viral load above 5,000 and CD4 cell counts below 300 on their current medications. Doctors have used several approaches to treat these types of HIV patients but it is not clear which approach is best.

OPTIMA is being conducted in VA hospitals in the US, and hospitals in the United Kingdom and Canada. Enrollment into the study started in June 2001 and will last until the end of 2005. Study participants are randomly assigned to one of four treatment groups: 1) Up to 4 anti-HIV drugs, 2) 5 or more anti-HIV drugs, 3) Stop anti-HIV drugs for 12 weeks and then restart with up to 4 drugs, and 4) Stop anti-HIV drugs for 12 weeks and then start with 5 or more drugs.

## An open-label randomized clinical trial of novel therapeutic strategies for HIV-infected patients in whom antiretroviral therapy has failed: rationale and design of the OPTIMA Trial

TASSOS C. KYRIAKIDES, PHD, ABDEL BABIKER, PHD, JOEL SINGER, PHD, WILLIAM CAMERON, MD, MARTIN T. SCHECHTER, MD, MARK HOLODNIY, MD, SHELDON T. BROWN, MD, MIKE YOULE, MD, BRIAN GAZZARD, MD, ON BEHALF OF THE OPTIMA STUDY TEAM

**Abstract:** OPTIMA (OPTions In Management with Antiretrovirals) is a clinical trial with a factorial randomization to evaluate the hypotheses that mega-antiretroviral therapy (ART) consisting of five or more anti-HIV drugs compared to standard-ART consisting of four or fewer anti-HIV drugs and a 3-month antiretroviral drug-free period (ARDFP) compared to no ARDFP will delay the occurrence of new or recurrent acquired immunodeficiency syndrome events or death, and prove to be more cost-effective in treating human immunodeficiency virus-infected individuals previously exposed to ART drugs from the current three main classes. The aim is to randomize 1700 participants to four treatment strategy arms: (1) ARDFP + standard-ART; (2) ARDFP + mega-ART; (3) no ARDFP + standard-ART; (4) no ARDFP + mega-ART. The planned study duration is 3.5 years with 2.5 years of intake and a minimum 1 year of follow-up. The OPTIMA Trial was initiated in June 2001 at 30 U.S. Department of Veterans' Affairs hospitals, 22 hospitals in Canada, and 25 hospitals in the United Kingdom. This is the first large-scale, multicenter, randomized controlled trial to compare the relative efficacy of these different therapeutic strategies. We discuss the rationale behind the OPTIMA Trial design as well as the issues arising from the conduct of a trial that involves three national clinical trial agencies.

*(Control Clin Trials 24:481-500, 2003)*
*CSPCC West Haven, CT*

# CSP #706D

# HIV Seroprevalence and Risks in Veterans with Severe Mental Illness

The HIV Seroprevalence and Risks in Veterans with Severe Mental Illness (SMI) study was a four-year longitudinal study of veterans with severe mental illness. This Durham ERIC study supplemented a collaborative study funded by the National Institute of Mental Health. The Durham VA was the only VA site represented in the study, and they collaborated with four non-VA sites. The objective of the study was to determine the prevalence of HIV and other related infections such as Hepatitis C, along with associated risk behaviors in veterans with SMI. SMI diagnoses include schizophrenia, schizoaffective disorder, bipolar disorder, and posttraumatic stress disorder (PTSD). HIV risk behaviors include injection drug use and sexual promiscuity, personal and social-contextual factors, and comorbid mental disorders.

The articles described below present results from the five-site health and risk study of blood-borne infections among persons with SMI as reported in a special section of *Psychiatric Services*.

## The Five-Site Health and Risk Study of Blood-Borne Infections Among Persons with Severe Mental Illness

STANLEY ROSENBERG, PHD, JEFFREY SWANSON, PHD, GEORGE WOLFORD, PHD, FRED OSHER, MD, MARVIN SWARTZ, MD, SUSAN ESSOCK, PHD, MARIAN BUTTERFIELD, MD, MPH, BRYAN MARSH, MD AND THE FIVE-SITE HEALTH AND RISK STUDY RESEARCH COMMITTEE

**Abstract:** The general problem of blood-borne diseases in the United States is reviewed in this article, particularly as it affects people with severe mental illness and those with comorbid substance use disorders. The epidemiology and natural history of three of the most important infections are reviewed: the human immunodeficiency virus (HIV), the hepatitis B virus, and the hepatitis C virus. Current knowledge about blood-borne diseases among people with SMI as well as information on current treatment advances for hepatitis C are summarized. A heuristic model, based on the pragmatic, empirical, and conceptual issues that influenced the final study design, is presented. The specific rationale of the five-site collaborative design is discussed, as well as the sampling frames, measures, and procedures used at the participating sites. Alternative strategies for analyzing data deriving from multisite studies that use nonrandomized designs are described and compared.

*(Psychiatric Services 54:827-835, 2003)*
*ERIC Durham, NC*

# Risk Factors for HIV, Hepatitis B, and Hepatitis C Among Persons with Severe Mental Illness

SUSAN ESSOCK, PHD, SHAUNA DOWDEN, PHD, NIEL CONSTANTINE, PHD, LEN KATZ, PHD,
MARVIN SWARTZ, MD, KEITH MEADOR, MD, MPH, FRED OSHER, MD, STANLEY ROSENBERG, PHD
AND THE FIVE-SITE HEALTH AND RISK STUDY RESEARCH COMMITTEE

**Abstract:** Previous reports have indicated that persons with severe mental illness (SMI) have an elevated risk of contracting HIV, hepatitis B, and hepatitis C compared with the general population. This study extends earlier findings by examining the factors that are most predictive of serologic status among persons with SMI.

A total of 969 persons with SMI from five sites in four states were approached to take part in an assessment involving testing for blood-borne infections and a one-time standardized interview containing questions about sociodemographic characteristics, substance use, risk behaviors for sexually transmitted diseases, history of sexually transmitted diseases, and health care.

The greater the number of risk behaviors, the greater was the likelihood of infections, both for persons in more rural locations (New Hampshire and North Carolina), where the prevalence of infection was lower, and those in urban locations (Hartford, CT; Bridgeport, CT; and Baltimore, MD), where the prevalence was higher. Although no evidence was found that certain behaviors increase a person's risk of one blood-borne infection while other behaviors increase the risk of a different infection, it is conceivable that more powerful research designs would reveal some significant differences among the risks.

Clinicians should be attentive to these risk factors so as to encourage appropriate testing, counseling, and treatment.

*(Psychiatric Services 54:836-841, 2003)*
*ERIC Durham, NC*

# Substance Abuse and the Transmission of Hepatitis C Among Persons with Severe Mental Illness

FRED OSHER, MD, RICHARD GOLDBERG, PHD, SCOT MCNARY, PHD, MARVIN SWARTZ, MD, SUSAN ESSOCK, PHD, MARIAN BUTTERFIELD, MD, MPH, STANLEY ROSENBERG, PHD AND THE FIVE-SITE HEALTH AND RISK STUDY RESEARCH COMMITTEE

**Abstract:** The authors sought to better understand the relationship of substance abuse to higher rates of transmission of hepatitis C among persons with severe mental illness.

The authors assessed 668 pers0ons with severe mental illness for HIV, hepatitis B, and hepatitis C infection through venipuncture. Demographic characteristics, substance abuse, and risk behaviors for blood-borne infections were assessed through interviews and collection of clinical data.

Eight-two percent of the assessed persons were not infected, and 18 percent had hepatitis C. Among those with hepatitis C infection, 546 (82 percent) tested negative for all viruses. Of the 122 (18 percent) who had hepatitis C, 53 (8 percent) had only hepatitis C, 56 (8 percent) had both hepatitis C and hepatitis B, three (1 percent) had hepatitis C and HIV, and ten (2 percent) had all three infections. More than 20 percent of the sample reported lifetime intravenous drug use, and 14 percent reported lifetime needle sharing. Fifty-seven percent had sniffed or snorted cocaine, and 39 percent had smoked crack. A stepwise regression model was used to identify interaction effects of these behaviors and risk of hepatitis C infection among persons with severe mental illness. Use of needles and of crack cocaine were associated with a large increase in the likelihood of hepatitis C infection.

The high rates of co-occurring substance use disorders among persons with severe mental illness, coupled with the role of substance abuse as the primary vector for hepatitis C transmission, warrants special consideration.

*(Psychiatric Services 54:842-847, 2003)*
*ERIC Durham, NC*

# Gender Differences in Hepatitis C Infection and Risks Among Persons with Severe Mental Illness

MARIAN BUTTERFIELD, MD, MPH, HAYDEN BOSWORTH, PHD, KEITH MEADOR MD, MPH, KAREN STECHUCHAK, MS, SUSAN ESSOCK, PHD, FRED OSHER, MD, LISA GOODMAN, PHD, JEFFREY SWANSON, PHD, LORI BASTIAN, MD, RONNIE HORNER, PHD, AND THE FIVE-SITE HEALTH AND RISK STUDY RESEARCH COMMITTEE

**Abstract:** The authors assessed gender differences in hepatitis C infection and associated risk behaviors among persons with severe mental illness.

The sample consisted of 777 patients (251 women and 526 men) from four sites. Across sites, the rate of hepatitis C infection among men was nearly twice that among women. Clear differences were noted in hepatitis C risk behaviors. Men had higher rates of lifetime drug-related risk behaviors: needle use (23.1 percent compared with 12.5 percent), needle sharing (17.6% compared with 7.7%), and crack cocaine use (45.2 % compared with 30.8%). Women had significantly higher rates of lifetime sexual risk behaviors: unprotected sex in exchange for drugs (17.8% compared with 11.2%), unprotected sex in exchange for money or gifts (30.6% compared with 17%), unprotected vaginal sex (94% compared with 89.7%), and anal sex (33.7% compared with 22.6%). Gender appeared to modify some sex risks. Unprotected sex in exchange for drugs increased the risk of hepatitis C seropositivity for both men and women. In the multivariate model, gender was not significantly associated with hepatitis C seropositivity after adjustment for other risk factors.

Gender differences in the lifetime rates of drug risks explain the higher rates of hepatitis C infection among men with severe mental illness.

*(Psychiatric Services 54:848-853, 2003)*
*ERIC Durham, NC*

# Regular Sources of Medical Care Among Persons with Severe Mental Illness at Risk of Hepatitis C Infection

MARVIN SWARTZ, MD, JEFFREY SWANSON, PHD, MICHAEL HANNON, MA, HAYDEN BOSWORTH, PHD, FRED OSHER, MD, SUSAN ESSOCK, PHD, STANLEY ROSENBERG, PHD AND THE FIVE-SITE HEALTH AND RISK STUDY RESEARCH COMMITTEE

**Abstract:** An estimated 19.6% of persons with severe mental illness are infected with the hepatitis C virus. Given the pressing need to identify and treat persons with severe mental illness who are at risk of hepatitis C infection and transmission, the authors sought to estimate the proportion of hepatitis C-positive and –negative persons with severe mental illness who have a regular source of medical care.

Data for this study were obtained from 777 adults with severe mental illness at four diverse geographic sites at which respondents with severe mental illness participated in a structured interview and laboratory testing for HIV infection, AIDS, hepatitis B infection, and hepatitis C infection.

In bivariate analyses, 54.2% of hepatitis C-positive and 62.5% of hepatitis C-negative study participants with severe mental illness had a regular source of medical care. In multivariate analyses in which potential confounders were statistically controlled for, hepatitis C-positive persons with severe mental illness were less than half as likely as hepatitis C-negative persons to have a regular source of care. Being older, married, insured, or employed or having self-reported health problems increased the likelihood of receiving care. Being black or male or living in a community with high exposure to community violence lowered those odds.

There is an urgent need to improve access to medical care for persons with severe mental illness, especially those who may be at high risk of or are already infected with the hepatitis C virus.

*(Psychiatric Services 54:854-859, 2003)*
*ERIC Durham, NC*

# Responding to Blood-Borne Infections Among Persons with Severe Mental Illness

MARY BRUNETTE, MD, ROBERT DRAKE, BRYAN MARSH, MD, WILLIAM TORREY, MD,
STANLEY ROSENBERG, PHD AND THE FIVE-SITE HEALTH AND RISK STUDY RESEARCH COMMITTEE

**Abstract:** The Five-Site Health and Risk Study estimated prevalence rates of blood-borne infections, including the human immunodeficiency virus (HIV), hepatitis B, and hepatitis C, and addressed risk factors and correlates of infection among persons with severe mental illness. In this final article of the special section in the issue of *Psychiatric Services*, the authors review public health recommendations and best practices and discuss the implications of these results for community mental health care of clients with severe mental illness. Standard public health recommendations could be modified for use by community mental health providers. In addition, expansion of integrated dual disorders treatments and improving linkage with specialty medical care providers are recommended.

*(Psychiatric Services 54:860-865, 2003)*
*ERIC Durham, NC*

# CSP #290

# Monotherapy of Hypertension

This study compared six different blood pressure lowering drugs and placebo to determine their individual effectiveness if each were administered as single-drug treatment for hypertension. The initial results published in 1993 (N. Engl. J. Med. 328:914-21, 1993), showed that patient characteristics such as age and race were strong predictors of which drug would be most successful. Patients who were unresponsive to the first drug were randomized to a second single-drug therapy. The results of this phase showed that switching to a second drug is as effective as the common practice of adding a second drug to the initial therapy. Patients who did not respond to the second drug received a combination of the two drugs. The results demonstrated that a combination of drugs, which were not successful when used individually, had a high probability of success in controlling blood pressure, particularly when the combination included a diuretic.

The article below reports additional results from the study.

## Response to Six Classes of Antihypertensive Medications by Body Mass Index in a Randomized Controlled Trial

BARRY J. MATERSON, MD, MBA; DAVID W. WILLIAMS, MS; DOMENIC J. REDA, PHD;
WILLIAM C. CUSHMAN, MD, FOR THE VETERANS AFFAIRS COOPERATIVE STUDY GROUP ON ANTIHYPERTENSIVE AGENTS

**Abstract:** Blood pressure increases with increasing body mass index (BMI) and BMI is linearly related to blood pressure in population studies. Obesity has been said to cause resistance to antihypertensive medications. We compared short-term and 1-year blood pressure response by BMI category and weight change with hydrochlorothiazide, atenolol, diltiazem-SR, captopril, clonidine, prazosin, or placebo in 1292 male veterans. Drug doses were titrated to achieve goal diastolic blood pressure <90mm Hg over 4-8 weeks. Patients who achieved goal blood pressure were maintained to 1 year. BMI did not predict change in systolic, diastolic or pulse pressures during titration for any drug. At 1 year obese patients (BMI >30) were 2.5 times more likely to have diastolic blood pressure controlled by atenolol than normal weight (BMI <27) patients (p=0.01). Only prazosin patients gained weight: 1.7 lb (end-titration, p<0.0001; 1-year, p=0.02). Obesity does not appear to cause resistance to antihypertensive medications.

*(J Clin Hypertens 5:197-201, 2003)*
*CSPCC Hines, IL*

# CSP #448

# A Randomized, Controlled, Blinded, Multicenter Trial to Assess the Efficacy of Protection from Natural Influenza Virus Infection of Influenza Virus Vaccine, Trivalent, Types A and B, Live, Cold-Adapted (CAIV-T) and Inactivated Influenza Virus Vaccine in Patients with Chronic Obstructive Pulmonary Disease (COPD): A Field Trial

The study was designed as a prospective, randomized, one-year, multicenter, double-blind trial. The participants are male and female veterans attending VA outpatient clinics or residing in VA nursing homes and domiciliaries who are at least 50 years of age and have pre-existing, clinically stable COPD. The target sample size is 4,000 subjects. Eligible volunteers were randomly assigned to receive one of two vaccination regimens: 1. intranasal CAIV-T with intramuscular inactivated influenza virus vaccine, or 2. intramuscular inactivated influenza virus vaccine with intranasal saline placebo. The sample size was calculated assuming a 5% attack rate for laboratory-documented influenza-caused illness in patients vaccinated with TVV alone, and a reduction in this rate by 50% with the combined vaccines. The sample size allows vaccine efficacy to be detectable with 80% power, setting the lower 95% confidence limit for vaccine efficacy at 15%.

## Efficacy Trial of Live, Cold-Adapted and Inactivated Influenza Virus Vaccines in Older Adults with Chronic Obstructive Pulmonary Disease: a VA Cooperative Study

GORSE GJ, O'CONNOR TZ, YOUNG SL, MENDELMAN PM, BRADLEY SF, NICHOL SL, STRICKLAND JH JR, PAULSON DM, RICE KL, FOSTER RA, FULAMBARKER AM, SHIGEOKA JW, KUSCHNER WG, GOODMAN RP, NEUZIL KM, WITTES J, BOARDMAN KD, PEDUZZI PN

**Abstract:** We assessed whether trivalent live, cold-adapted influenza virus (CAIV-T) vaccine provides added protection when co-administered with trivalent inactivated influenza virus vaccine (TVV) in patients with chronic obstructive pulmonary disease (COPD). Subjects (N=2215) were randomly assigned to receive either TVV intramuscularly (IM) and CAIV-T intranasally (TC), or TVV and placebo (TP). The vaccines were well-tolerated. Efficacy of TC compared to TP was not statistically significant and was 0.16 for any influenza virus strain (95% confidence limit (CL): -0.22, 0.43), 0.26 for A (H3N2) virus (95% CL: -0.17, 0.53), and -0.05 for type B virus (95% CL: -1.13, 0.48). However, there was a possible advantage for TC over TP in reducing respiratory consequences of an influenza season measured by pulmonary function and symptoms at end of study.

*(Vaccine 21:2133-2144, 2003)*
*VA CRPCC Albuquerque, NM and* CSPCC West Haven, CT

The influenza vaccine study tested the effectiveness of the flu shot plus a nasal spray administered flu vaccine (combination) with the flu shot alone (single) to prevent influenza in older adults with chronic obstructive pulmonary disease (COPD). The study enrolled 2215 veterans in 20 VA Medical Centers between October 1998 and January 1999. 1107 veterans received the flu shot plus the nasal spray and 1108 received the flu shot alone. Overall, there was no significant difference between the two vaccine groups in preventing influenza.

This sub-study compared the clinical characteristics associated with influenza in 94 subjects who had laboratory documented flu to the clinical characteristics in 491 subjects who had other respiratory infections during the 1998-1999 flu season. We found that only fever and muscle aches and pains occurred more often in the influenza group than in the group with other respiratory infections. Overall, clinical characteristics were poor predictors of laboratory documented influenza in these older, vaccinated patients with chronic lung disease.

## Recognizing Influenza in Older Patients with Chronic Obstructive Pulmonary Disease Who Have Received Influenza Vaccine

KATHLEEN M. NEUZIL, THERESA Z. O'CONNOR, GEOFFREY J. GORSE, AND KRISTIN L. NICHOL

**Abstract:** A substudy analysis was conducted to determine the clinical characteristics associated with symptomatic, laboratory-documented influenza (LDI) among 2215 veterans with chronic obstructive pulmonary disease who participated in Department of Veterans Affairs Cooperative Study 448 and who received trivalent inactivated influenza virus vaccine with or without intranasal live-attenuated, cold-adapted influenza vaccine. Of 585 evaluable first occurrences of acute respiratory illnesses, 94 (16%) were LDI. Respiratory symptoms of cough, sputum production, and dyspnea occurred in >90% of patients with LDI; 68% had documented or subjective fever, and 81% had myalgias. Stepwise logistic regression identified only fever and myalgia as being statistically associated with LDI. During the influenza outbreak period, the positive predictive value of fever and myalgia was 41%. Clinical criteria were poor predictors of LDI in these older, vaccinated patients with chronic lung disease. Additional studies are warranted to define optimal methods for the diagnosis of influenza among older persons with chronic obstructive pulmonary disease.

*(Clin Infect Dis 36:169-74, 2003)*
*CSPCC West Haven, CT*

# CSP #391

# Effect of Polyunsaturated Lecithin on Liver Fibrosis

This study was designed to evaluate the effectiveness of polyenylphosphatidylcholine (PPC) in preventing the progression to cirrhosis in long-term heavy drinkers with alcoholic liver fibrosis, the early stage of liver disease. At the time of entry, study patients had been drinking on average 16 drinks/day for 19 years. However, patients reduced their alcohol intake to an average of 2.5 drinks/day while on the study. This remarkable reduction was sustained over the course of follow-up and was also observed in patients who eventually dropped out of the study. The reduction in drinking was an unexpected outcome and was attributed to the support structures provided by the study follow-up. These featured monthly clinic visits with a supportive dedicated study nurse who was also regularly available between visits, and brief physician visits with more extensive physical exams every six months. The enhanced levels of overall medical care provided by the follow-up structure incorporated the essential and objective features of "brief intervention" approaches shown to be effective in other settings. The study showed for the first time that these approaches were associated with reductions in drinking sustained beyond one year.

## I. Veterans Affairs Cooperative Study of Polyenylphosphatidylcholine in Alcoholic Liver Disease: Effects on Drinking by Nurse/Physician Teams

CHARLES S. LIEBER, DAVID G. WEISS, ROBERTO GROSZMANN, FIORENZO PARONETTO, AND STEVEN SCHENKER, FOR THE VETERANS AFFAIRS COOPERATIVE STUDY 391 GROUP

**Abstract:** *Background:* This multicenter prospective, randomized, double-blind placebo-controlled trial was designed to evaluate the effectiveness of polyenylphosphatidylcholine against the progression of liver fibrosis toward cirrhosis in alcoholics. Seven hundred eighty-nine alcoholics with an average intake of 16 drinks per day were enrolled. To control excessive drinking, patients were referred to a standard 12-step-based alcoholism treatment program, but most patients refused to attend. Accordingly, study follow-up procedures incorporated the essential features of the brief-intervention approach. An overall substantial and sustained reduction in drinking was observed. Hepatic histological and other findings are described in a companion article.

*Methods*: Patients were randomized to receive daily three tablets of either polyenylphosphatidylcholine or placebo. Monthly follow-up visits included an extensive session with a medical nurse along with brief visits with a study physician (hepatologist or gastroenterologist). A detailed physical examination occurred every 6 months. In addition, telephone consultations with the nurse were readily available. All patients had a liver biopsy before entry; a repeat biopsy was scheduled at 24 and 48 months.

*Results*: There was a striking decrease in average daily alcohol intake to approximately 2.5 drinks per day. This was sustained over the course of the trial, lasting from 2 to 6 years. The effect was similar both in early dropouts and long-term patients, i.e., those with a 24-month biopsy or beyond.

*Conclusions*: In a treatment trial of alcoholic liver fibrosis, a striking reduction in alcohol consumption from 16 to 2.5 daily drinks was achieved with a brief-intervention approach, which consisted of a relative economy of therapeutic efforts that relied mainly on treatment sessions with a medical nurse accompanied by shorter reinforcing visits with a physician. This approach deserves generalization to address the heavy drinking problems commonly encountered in primary care and medical speciality practices.

*(Alcohol Clin Exp Res 27(11):1757-1764, 2003)*
*CSPCC Perry Point, MD*

Subjects with liver fibrosis determined at biopsy were assigned to receive either PPC or matching placebo with repeat biopsy (primary outcome measure) at 24 months to assess the effects of PPC on the progression of liver fibrosis based on change in histologic staging. As reported below, the effects of PPC were seen not to be different from placebo in preventing the progression to cirrhosis by stage. The evaluation of PPC was complicated by two unanticipated trends in study patients: the dropout rate was much higher than planned for (412 of 789 patients completed 24 month biopsy) and there was a substantial sustained reduction in drinking in patients while on study from an average of 16 drinks/day to 2.5 drinks/day.

## II. Veterans Affairs Cooperative Study of Polyenylphosphatidylcholine in Alcoholic Liver Disease

CHARLES S. LIEBER, DAVID G. WEISS, ROBERTO GROSZMANN, FIORENZO PARONETTO, AND STEVEN SCHENKER, FOR THE VETERANS AFFAIRS COOPERATIVE STUDY 391 GROUP

**Abstract**: *Background:* Polyenylphosphatidylcholine (PPC) has been shown to prevent alcoholic cirrhosis in animals. Our aims were to determine the effectiveness of PPC in preventing or reversing liver fibrosis in heavy drinkers and to assess the extent of liver injury associated with the reduced drinking achieved in these patients.

*Methods*: This randomized, prospective, double-blind, placebo-controlled clinical trial was conducted in 20 Veterans Affairs Medical Centers with 789 patients (97% male; mean age, 48.8 years) averaging 16 drinks per day (1 drink = 14 g of alcohol) for 19 years. A baseline liver biopsy confirmed the presence of perivenular or septal fibrosis or incomplete cirrhosis. They were randomly assigned either PPC or placebo. Liver biopsy was repeated at 24 months, and the main outcome measure was the stage of fibrosis compared with baseline. Progression was defined as advancing to a more severe stage.

*Results*: The 2-year biopsy was completed in 412 patients. PPC did not differ significantly from placebo in its effect on the main outcome. Alcohol intake was unexpectedly reduced in both groups to approximately 2.5 drinks per day. With this intake, 21.4% advanced at least one stage (22.8% of PPC patients and 20.0% of placebo patients). The hepatitis C virus-positive subgroup exhibited accelerated progression. Improvement in transaminases and bilirubin favoring PPC was seen at some time points in other subgroups (hepatitis C virus-positive drinkers or heavy drinkers).

*Conclusions*: PPC treatment for 2 years did not affect progression of liver fibrosis. A trend in favor of PPC was seen for transaminases and bilirubin (in subgroups). One of five patients progressed even at moderate levels of drinking, and thus health benefits commonly associated with moderate drinking do not necessarily extend to individuals in the early stages of alcoholic liver disease.

*(Alcohol Clin Exp Res 27(11):1765-1772, 2003)*
*CSPCC Perry Point, MD*

# CSP #505

# Millennium Cohort Study

In the report to the Committee on National Security, House of Representatives and the Armed Services Committee, U.S. Senate on Effectiveness of Medical Research Initiatives Regarding Gulf War Illnesses, the DoD identified the need for a coordinated capability to apply epidemiological research to determine whether deployment-related exposures are associated with post-deployment health outcomes. The Millennium Cohort Study, a prospective study of U.S. military forces, responds to this need and to recent recommendations from the Institute of Medicine to systematically collect population-based demographic and health data to evaluate the health of service personnel throughout their military careers and after leaving military service.

This study will follow about 140,000 members of the U.S. Armed Forces while they are on active duty and beyond. The health status of persons deployed and not deployed will be compared to assess the effects of deployment on health in the short-term and long-term. The study began in the year 2000 and is planned to continue until the year 2022. A mailed and internet-based questionnaire survey will be used to assess the health of participating individuals at 3-year intervals. The expected benefits of the study are the identification of illness associated with military deployments and exposures specifically responsible for these illnesses. This information will be used to develop preventive measures with the ultimate aim being protection of the health of members of the U.S. Armed Forces who are deployed.

## The Millennium Cohort Study: a 21-year prospective study of 140,000 military personnel

CHESBROUGH KB, AMOROSO P, BOYKO EJ, GACKSTETTER GD, RIDDLE JR, RYAN MAK, HOOPER TI, GRAY GC

**Abstract**: *Objectives*: To follow a cohort of active duty members of the U.S. military during and after military service to assess the effects of military service on health.

*Research Plan and Methods*: The Millennium Cohort study is a probability-based, cross-sectional sample of 100,000 U.S. military personnel (as of October 2000) who will be followed prospectively by postal surveys every 3 years over a 21 -year period. The 100,000 persons will be comprised of 50,000 veterans who have been deployed to Southwest Asia, Bosnia, or Kosovo since August 1997, and 50,000 veterans who have not been deployed to these conflicts. In October 2004 and October 2007, 20,000 new military personnel will be added to the cohort. The total of 140,000 veterans will be followed until the year 2022.

*Findings*: As of September 2003, over 77,000 have agreed to participate in this study and have completed baseline questionnaire surveys. Planning is currently underway for the 2004 survey. It will

contain questions on demographic characteristics, self-reported medical conditions and symptoms, smoking behaviors, diet, and exercise, and will utilize validated instruments to capture self-assessed physical and mental well being (SF-36V), mental health diagnoses (Patient Health Questionnaire), and posttraumatic stress disorder (PCL- 17). The primary objective for this study is to compare change in health status between deployed and non-deployed personnel and the adjusted incidence rates of chronic disease between cohorts. Secondary objectives include comparing the adjusted change in health between the cohorts as reflected by SF-36V scores and the Patient Health Questionnaire diagnostic assessment.

This study will serve as a foundation upon which other routinely captured medical and deployment data may be added to answer future questions regarding the health risks of military deployment, military occupations, and general military service.

*(Mil Med 167:483-488, 2002)*
*ERIC Seattle, WA*

# CSP #334

# A Psychophysiological Study of Chronic Post-Traumatic Stress Disorder in Vietnam Veterans

This multisite study tested the ability of psychophysiological responding to predict posttraumatic stress disorder (PTSD) diagnosis (current, lifetime, or never) in a large sample of male Vietnam veterans. Predictor variables for a logistic regression equation were drawn from a challenge task involving scenes of combat. The equation was tested and cross-validated demonstrating correct classification of approximately 2/3 of the current and never PTSD participants. Results replicate the finding of heightened psychophysiological responding to trauma-related cues by individuals with current PTSD, as well as differences in a variety of other domains between groups with and without the disorder. Follow-up analyses indicate that veterans with current PTSD who do not react physiologically to the challenge task manifest less reexperiencing symptoms, depression, and guilt. Discussion addresses the value of psychophysiological measures for assessment of PTSD.

## Predictors of Emotional Numbing, Revisited: A Replication and Extension

WILLIAM F. FLACK, JR., BRETT T. LITZ, FRANK Y. HSIEH, DANNY G. KALOUPEK, AND TERENCE M. KEANE

**Abstract:** Litz et al. (1997), theorizing that emotional numbing (EN) is the result of emotional depletion caused by chronic hyperarousal, demonstrated that a cluster of hyperarousal symptoms was a robust predictor of EN symptoms. In the present study, these findings were replicated and extended in two multiple regression analyses of data from a large, multisite investigation (T. M. Keane et al., 1998) of psychophysiological responding by male combat veterans. The arousal (D) cluster of symptoms was again the most robust predictor of EN symptoms, whereas physiological indices of arousal and reactivity accounted for negligible amounts of variance in both regression equations. These findings underscore the possible link between disturbances related to arousal and the capacity of traumatized individuals to express and experience pleasant feelings.

*(Journal of Traumatic Stress 13(4): 611-618, 2000)*
*CSPCC Palo Alto, CA*

# Peritraumatic Dissociation and Physiological Response to Trauma-relevant Stimuli in Vietnam Combat Veterans with Posttraumatic Stress Disorder

ML KAUFMAN, MO KIMBLE, DG KALOUPEK, LM MCTEAGUE,
P BACHRACH, AM FORTI, AND TM KEANE

**Abstract:** A recent study found that female rape victims with acute posttraumatic stress disorder (PTSD) who received a high score on the Peritraumatic Dissociative Experiences Questionnaire exhibited suppression of physiological responses during exposure to trauma-related stimuli. The goal of our present study was to test whether the same relationship holds true for male Vietnam combat veterans with chronic PTSD, using secondary analyses applied to data derived from a Veteran's Affairs Cooperative Study. Vietnam combat veterans (N = 1238) completed measures to establish combat-related PTSD diagnostic status, extent of PTSD-related symptomatic distress, and presence of dissociative symptoms during their most stressful combat-related experiences. Extreme subgroups of veterans with current PTSD were classified as either low dissociators (N = 118) or high dissociators (N = 256) based on an abbreviated version of the Peritraumatic Dissociative Experiences Questionnaire. Dependent variables reflected subjective distress along with heart rate, skin conductance, electromyographic, and blood pressure data when responding to neutral and trauma-related audiovisual and imagery presentations. Veterans in the current PTSD group had significantly higher dissociation scores than did veterans in the lifetime and never PTSD groups. Among veterans with current PTSD, high dissociators reported greater PTSD-related symptomatic distress than did low dissociators, but the groups did not differ with respect to physiological reactivity to the trauma-related laboratory presentations. Our results replicate the previously reported relationship between peritraumatic dissociation and PTSD status in Vietnam combat veterans. However, we found no association between peritraumatic dissociation and the extent of physiological responding to trauma-relevant cues in male veterans with chronic combat-related PTSD.

*(J Nerv Ment Dis 190(3):167-74, 2002)*
*CSPCC Palo Alto, CA*

# CSP #420

# Group Treatment of PTSD

The study is a randomized clinical trial of a treatment that we consider to be the most promising approach for treating war-zone-related PTSD. The primary objective of the study was to evaluate the efficacy of Trauma Focused Group Therapy (TFGT) for treating PTSD symptoms. Secondary objectives were to test the effect of TFGT on other psychiatric symptoms, functional impairment, physical health, and utilization of physical and mental health services.

Three hundred sixty male outpatients with PTSD related to service in the Vietnam theater were randomized to either TFGT or Present Centered Group Therapy (PCGT), each of which were delivered in weekly 1.5 or 2 hr group therapy sessions for 30 weeks. Group booster sessions were delivered monthly for the 22 weeks following active treatment. All subjects received case management throughout the time they participated in the study.

This study did not find a treatment effect for trauma-focused group therapy. The difference between the effectiveness and adequate dose findings suggests the possible value of methods to enhance the delivery of cognitive-behavioral treatments in clinical practice settings.

## Randomized Trial of Trauma-Focused Group Therapy for Posttraumatic Stress Disorder: Results From a Department of Veterans Affairs Cooperative Study

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**Abstract:** *Background:* Department of Veterans Affairs Cooperative Study 420 is a randomized clinical trial of 2 methods of group psychotherapy for treating posttraumatic stress disorder (PTSD) in male Vietnam veterans.

*Methods:* Vietnam veterans (360 men) were randomly assigned to receive trauma-focused group psycho-therapy or a present-centered comparison treatment that avoided trauma focus. Treatment was provided weekly to groups of 6 members for 30 weeks, followed by 5 monthly booster sessions. Severity of PTSD was the primary outcome. Additional measures were other psychiatric symptoms, functional status, quality of life, physical health, and service utilization. Follow-up assessments were conducted at the end of treatment (7 months) and at the end of the booster sessions (12 months); 325 individuals participated in 1 or both assessments. Additional follow-up for PTSD severity was performed in a subset of participants at 18 and 24 months.

*Results:* Although post-treatment assessments of PTSD severity and other measures were significantly improved from baseline, intention-to-treat analyses found no overall differences between therapy groups on any outcome. Analyses of data from participants who received an adequate dose of treatment suggested that trauma-focused group therapy reduced avoidance and numbing and, possibly, PTSD symptoms. Dropout from treatment was higher in trauma-focused group treatment. Average improvement was modest in both treatments, although approximately 40% of participants showed clinically significant change.

*Conclusions:* This study did not find a treatment effect for trauma-focused group therapy. The difference between the effectiveness and adequate dose findings suggests the possible value of methods to enhance the delivery of cognitive-behavioral treatments in clinical practice settings.

*(*Arch Gen Psychiatry *60:481- 489, 2003)*
*CSPCC Palo Alto, CA*

# CSP #97-010

# Post-Traumatic Stress Disorder (PTSD)

This paper on post-traumatic stress disorder (PTSD) in women veterans was conducted as part of a larger VA funded study of Veteran Women's Alcohol Problems. In this study, women veterans who used the Women's Clinic at the VA Puget Sound Health Care system were invited to complete one or more mail surveys that asked questions about their past health, current health status, and health practices. The survey was mailed in 1998, 1999, and 2000. Detailed in-person interviews about PTSD and drinking behaviors were conducted on a subset of women who completed the surveys. This study has resulted in numerous papers about PTSD, drinking, and other aspects of women's health.

## Screening for Post-Traumatic Stress Disorder in Female Veteran's Patients: Validation of the PTSD Checklist

DOBIE DJ, KIVLAHAN DR, MAYNARD C, BUSH KR, MCFALL M, EPLER AJ, BRADLEY KA

**Abstract:** We evaluated the screening validity of a self-report measure for post-traumatic stress disorder (PTSD), the PTSD Checklist (PCL), in female Veterans Affairs (VA) patients. All women seen for care at the VA Puget Sound Health Care system from October 1996-January 1999 (n=2,545) were invited to participate in a research interview. Participants (n=282) completed the 17-item PCL, followed by a gold standard diagnostic interview for PTSD, the Clinician Administered PTSD Scale (CAPS). Thirty-six percent of the participants (n=100) met CAPS diagnostic criteria for current PTSD. Receiver Operating Characteristic (ROC) analysis was used to evaluate the screening performance of the PCL. The area under the ROC curve was 0.86 (95% CI 0.82-0.90). A PCL score of 38 optimized the performance of the PCL as a screening test (sensitivity 0.79, specificity 0.79). The PCL performed well as a screening measure for the detection of PTSD in female VA patients.

*(Gen Hosp Psychiat 24:367-374, 2002)*
*ERIC Seattle, WA*

# CSP #97-010

# Respiratory Viruses

To understand health care use among adults during flu season, we identified a cohort of veterans who were 18 years and older and used Department of Veterans Affairs (VA) facilities in Oregon and Washington states during 1998–2000. Using VA data sources, we determined the number of acute cardiopulmonary hospitalizations and primary care and urgent care visits.

## Winter Respiratory Viruses And Health Care Use: A Population-Based Study In The Northwest United States

NEUZIL KM, MAYNARD C, GRIFFIN MR, HEAGERTY P

**Abstract**: To quantify health care use among adults during influenza and respiratory syncytial virus (RSV) seasons, we identified a cohort of veterans aged >/=18 years who used Department of Veterans Affairs (VA) facilities in Oregon and Washington states as their source of health care. During 1998-2000, veterans accrued 237,159 person-years of follow-up. Using VA data sources, we measured acute cardiopulmonary hospitalizations and primary care and urgent care visits. Differences between rates of study events when influenza and/or RSV were circulating and event rates when neither virus was circulating were used to calculate winter virus-attributable morbidity. Inpatient and outpatient event rates were consistently higher during winter virus season, compared with non-winter virus season. Annual rates of cardiopulmonary hospitalizations attributable to influenza or RSV infection ranged from 0.8 (95% confidence interval [CI], 0.1-1.5) per 1000 low-risk individuals aged 18-49 years, to 10.6 (95% CI, 7.5-13.6) per 1000 high-risk individuals aged >/=65 years. Each year, circulation of influenza and RSV coincide with predictable increases in medical care use.

*(Clin Infect Dis 37:201-207, 2003)*
*ERIC Seattle, WA*

# CSP #366

# A Genetic Linkage Study of Schizophrenia

Several reports have suggested that there may be a gene on chromosome 13 that is more common in persons that become schizophrenic than in persons that do not become schizophrenic. Genetic data from 166 families with at least two schizophrenic siblings was analyzed using a statistical technique called linkage analysis to see if similar results would be found in these families. The families had various ethnic backgrounds. Sixty-two families could be described as northern European – American, and 60 could be described as African-American. Analysis using all of the families did find similar results. Analyses using the northern European-American families separately and the African-American families separately also found similar results.

## Linkage of Chromosome 13q32 to Schizophrenia in a Large Veterans Affairs Cooperative Study Sample

STEPHEN V. FARAONE, ANDREW D. SKOL, DEBBY W. TSUANG, STEPHEN BINGHAM, KEITH A. YOUNG, SARITA PRABHUDESAI, SUSAN L. HAVERSTOCK, FELICITAS MENA, AERATH SRI KUMAR MENON, DARREN BISSET, JOHN PEPPLE, FRED SAUTTER, CHARLENE BALDWIN, DAVID WEISS, JOSEPH COLLINS, TIM KEITH, MICHAEL BOEHNKE, MING T. TSUANG, AND G.D. SCHELLENBERG

**Abstract**: Several prior reports have suggested that chromosomal region 13q32 may harbor a schizophrenia susceptibility gene. In an attempt to replicate this finding, we assessed linkage between chromosome 13 markers and schizophrenia in 166 families, each with two or more affected members. The families, assembled from multiple centers by the Department of Veterans Affairs Cooperative Studies Program, included 392 sampled affected subjects and 216 affected sib pairs. By DSM-III-R criteria, 360 subjects (91.8%) had a diagnosis of schizophrenia, and 32 (8.2%) were classified as schizoaffective disorder, depressed. The families had mixed ethnic backgrounds. The majority were northern European-American families ($n = 62$, 37%), but a substantial proportion were African-American kindreds ($n = 60$, 36%). Chromosome 13 markers, spaced at intervals of approximately 10 cM over the entire chromosome and 2-5 cM for the 13q32 region were genotyped and the data analyzed using semi-parametric affected only linkage analysis. For the combined sample (with race broadly defined and schizophrenia narrowly defined) the maximum LOD score was 1.43 ($Z$-score of 2.57; $P = 0.01$) at 79.0 cM between markers D13S1241 (76.3 cM) and D13S159 (79.5 cM). Both ethnic groups showed a peak in this region. The peak is within 3 cM of the peak reported by Brzustowicz et al. [1999: Am J Hum Genet 65:1096-1103].

*(Am J Med Genet 114:598-604, 2002)*
*CSPCC Perry Point, MD*

Investigators who studied 80 British families with schizophrenia found a gene complex called NOTCH4 that had abnormalities that were more likely to be found in an ill child of an ill parent than in a well child. Genetic data from 166 families was analyzed for characteristics called linkage and association to determine if similar results would be found in these families. These families included 392 ill persons and 216 pairs of ill siblings. Sixty-two families were European American, and 60 families were African American. There was moderate evidence of linkage in an analysis that used all of the families. The abnormalities that were more likely to be found in an ill child were observed to be more likely only in the African American families in this study.

## Modest Evidence for Linkage and Possible Confirmation of Association Between NOTCH4 and Schizophrenia in a Large Veterans Affairs Cooperative Studies Sample

A.D. SKOL, K.A. YOUNG, D.W. TSUANG, S.V. FARAONE, S.L., HAVERSTOCK, S. BINGHAM, S. PRABHUDESAI, F. MENA, A.S. MENON, CHANG-EN YU, PAUL RUNDELL, J. PEPPLE, F. SAUTER, C. BALDWIN, D. WEISS, J. COLLINS, T. KEITH, M. BOEHNKE, G.D. SCHELLENBERG, AND M.T. TSUANG

**Abstract**: Wei and Hemmings [2000: Nat Genet 25:376-377], using 80 British parent-offspring trios, identified a number of NOTCH4 variants and haplotypes that showed statistically significant evidence of association to schizophrenia. Specifically, the 10 repeat allele of a $(CTG)_n$ marker and the 8 repeat allele of a $(TAA)_n$ marker demonstrated excess transmission to affected individuals; SNP2[1] and haplotypes SNP2-$(CTG)_n$ and SNP1[2]-SNP2-$(CTG)_n$ also showed significant associations. In an attempt to replicate these findings, we tested for linkage and association between the same five markers used by Wei and Hemmings in 166 families collected from a multi-center study conducted by the Department of Veterans Affairs (DVA) Cooperative Study Program (CSP). The families include 392 affected subjects (schizophrenia or schizoaffective disorder, depressed) and 216 affected sibling pairs. The families represent a mix of European Americans (n = 62, 37%), African Americans (n = 60, 36%), and racially mixed or other races (n = 44, 27%). We identified moderate evidence for linkage in the pooled race sample (LOD = 1.25) and found excess transmission of the 8 ($P$ = 0.06) and 13 ($P$ = 0.04) repeat alleles of the $(TAA)_n$ marker to African American schizophrenic subjects. The 8 and 13 repeat alleles were previously identified to be positively associated with schizophrenia by Wei and Hemmings [2000: Nat Genet 25:376-377] and Sklar et al. [2001: Nat Genet 28:126-128], respectively.

*(Am J Med Genet 118B:8-15, 2003)*
*CSPCC Perry Point, MD*

# CSP #451
# The Clinical and Economic Impact of Olanzapine in the Treatment of Schizophrenia

Although new drugs are being frequently used for the treatment of schizophrenia, the long-term cost and benefit of one of these new drugs has not been compared to one of the older drugs. Three hundred nine patients with schizophrenia were entered into a trial between June 1998 and June 2000 at 17 Veterans Affairs Medical Centers. One hundred fifty-nine were to get the new drug, and one hundred fifty were to get the old drug. Each patient was to be in the trial for 12 months. Quality of life, thinking ability, symptoms of disease, adverse events, and costs for care were measured for each patient. There were few significant differences between the two groups. One type of adverse event was less often observed in the group assigned to the new drug. Thinking ability was slighter better in the group assigned to the new drug. Patients assigned to the new drug were more likely to gain weight, and the costs for patients with the new drug were higher than for the group assigned to the older drug.

## Effectiveness and Cost of Olanzapine and Haloperidol in the Treatment of Schizophrenia: A Randomized Controlled Trial

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**Abstract:** *Context*: Although olanzapine has been widely adopted as a treatment of choice for schizophrenia, its long-term effectiveness and costs have not been evaluated in a controlled trial in comparison with a standard antipsychotic drug.

*Objective*: To evaluate the effectiveness and cost impact of olanzapine compared with haloperidol in the treatment of schizophrenia.

*Design and Setting*: Double-blind, randomized controlled trial with randomization conducted between June 1998 and June 2000 at 17 US Department of Veterans Affairs medical centers.

*Participants*: Three hundred nine patients with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnosis of schizophrenia or schizoaffective disorder, serious symptoms, and serious dysfunction for the previous 2 years. Fifty-nine percent fully completed and 36% partially completed follow-up assessments.

*Interventions*: Patients were randomly assigned to receive flexibly dosed olanzapine, 5 to 20 mg/d, with prophylactic benztropine, 1 to 4 mg/d (n = 159); or haloperidol, 5 to 20 mg/d (n=150), for 12 months.

*Main Outcome Measures*: Standardized measures of symptoms, quality of life, neurocognitive status, and adverse effects of medication. Veterans Affairs administrative data and interviews concerning non-VA service use were used to estimate costs from the perspective of the VA health care system and society as a whole (i.e., consumption of all resources on behalf of these patients).

*Results*: There were no significant differences between groups in study retention; positive, negative, or total symptoms of schizophrenia; quality of life; or extrapyramidal symptoms. Olanzapine was associated with reduced akathisia in the intention-to-treat analysis (P < .001) and with lower symptoms of tardive dyskinesia in a secondary analysis including only observations during blinded treatment with study drug. Small but significant advantages were also observed on measures of memory and motor function. Olanzapine was also associated with more frequent reports of weight gain and significantly greater VA costs, ranging from $3000 to $9000 annually. Differences in societal costs were somewhat smaller and were not significant.

*Conclusion:* Olanzapine does not demonstrate advantages compared with haloperidol (in combination with prophylactic benztropine) in compliance, symptoms, extrapyramidal symptoms, or overall quality of life, and its benefits in reducing akathisia and improving cognition must be balanced with the problems of weight gain and higher cost.

*(JAMA 290(20):2693-2702, 2003)*
*CSPCC Perry Point, MD*

# CSP #5

# Processes, Structures, and Outcomes of Care in Cardiac Surgery

This study is designed to find and demonstrate links between the process and structure of cardiac surgical care and the outcome of that care. To improve quality of care, it is essential to know what aspects of care and its delivery are most important to outcome. Knowledge from this study should enable cardiac surgery units to focus quality improvement efforts to enhance patient outcomes.

The article below assesses the relation of preoperative evaluations, intraoperative care, and supervision by senior physicians on perioperative mortality and morbidity after adjusting for preoperative patient risk factors.

## Relationship Between Processes of Care and Coronary Bypass Operative Mortality and Morbidity

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**Abstract:** *Background:* Information is limited regarding the effects of processes of care on cardiac surgical outcomes. Correspondingly, many recommended cardiac surgical processes of care are derived from animal experiments or clinical judgment. This report from the VA Cooperative Study in Health Services, "Processes, Structures, and Outcomes of Care in Cardiac Surgery," focuses on the relationships between 3 process groups (preoperative evaluation, intraoperative care, and supervision by senior physicians) and a composite outcome, perioperative mortality and morbidity.

*Methods:* Data on 734 risk, process, and structure variables were collected prospectively on 3988 patients who underwent coronary artery bypass grafting at 14 VA medical centers between 1992 and 1996. Data reduction was accomplished by examining data completeness and variation across sites and surgeon, using previously published data and clinical judgment. We then applied multivariable logistic regression to the 39 remaining processes of care to determine which were related to the composite outcome after adjusting for 17 patient-related risk factors and controlling for intraoperative complications.

*Results:* Our first analysis showed several measures of operative duration, the use of

Inotropic agents, transesophageal echo, lowest systemic temperature, and hemoconcentration/ultrafiltration, to be powerful predictors of the composite outcome. Because the use of inotropic agents and operative duration may be related to an intermediate outcome (eg, intraoperative complications), we performed a second analysis omitting these processes. The use of intraoperative transesophageal echo and hemoconcentration/ultrafiltration remained significantly associated with an increased risk of an event (odds ratios 1.60 and 1.36, respectively).

*Conclusions:* Our results viewed in the context of past studies suggest the possibility that inotropic use, TEE, and hemoconcentration ultrafiltration may have adverse effects on operative outcome. Further evaluation of these processes of care using observational data, as well as randomized trials when feasible, would be of interest.

*(Med Care 42: 59-70, 2004)*
*CSPCC Hines, IL*

# CSP #456

# Tension Free Inguinal Hernia Repair: Comparison of Open and Laparoscopic Surgical Techniques

Inguinal hernia is one of the most common worldwide afflictions of men. The presence of an inguinal hernia is indication for its repair. Approximately 700,000 hernia repairs are performed in the U.S. each year, and this procedure accounts for 10% of all general surgery procedures in the Veterans Health Administration (VHA) (10,000 inguinal herniorrhaphies performed per year). There are many different techniques currently in use for repairing inguinal hernias, and with the advent of laparoscopy, yet another technique is being advocated. Laparoscopic repair has been reported in some studies to be superior to open repair because of less pain and earlier return to work. However, laparoscopic repair requires a general or regional anesthetic and expensive equipment and supplies to perform. There is also evidence that open tension-free mesh repair may have results similar to laparoscopic repair for these patient-centered outcome measures. The general acceptance of this procedure, especially in the VHA, has not been uniform. Furthermore, no randomized trial of sufficient size and power to be conclusive has been done to set forth the operative "gold standard" for hernia repair. The objective of this study is to determine whether open tension-free herniorrhaphy, when compared with laparoscopic herniorrhaphy, can achieve equal or better recurrence rates and lower costs while achieving equivalent outcomes for patient-centered measures.

The first article is an introduction for the two following articles and how they fit together to summarize the status of the research for inguinal hernia. The second article describes the rationale for and the design of a multicenter, randomized, controlled clinical trial that is the result of a cooperative effort of the American College of Surgeons, Northwestern University, Creighton University, and the Hines VA Cooperative Studies Program Coordinating Center. The third article compares open tension-free inguinal hernia repair with preperitoneal laparoscopic inguinal hernia repair on recurrence rates at 2 years.

## Introduction: Inguinal Hernia Management—Testing Management Strategies in Two Clinical Trials

OLGA JONASSON, MD, FACS

This is an introduction for the two following articles and how they fit together to summarize the status of the research for inguinal hernia.

*(J Am Coll Surg 196:735-736, 2003)*
*CSPCC Hines, IL*

# The Development of a Clinical Trial to Determine if Watchful Waiting Is an Acceptable Alternative to Routine Herniorrhaphy for Patients with Minimal or No Hernia Symptoms

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Abstract: *Background:* This article describes the development and implementation of a randomized clinical trial designed to answer the question: Is watchful waiting an acceptable alternative to operation for men with asymptomatic or minimally symptomatic inguinal hernias?

*Study Design:* A clinical trial has been designed to compare watchful waiting and operation for men with an asymptomatic or a relatively asymptomatic inguinal hernia. Men are randomized to watchful waiting or a standard open operation, the Lichtenstein tension-free hernia repair, and are followed for a minimum of 2 years. The target sample size of 753 patients was chosen so that the trial would have power sufficiently high to detect a clinically meaningful difference between treatment groups in either of the two primary outcomes as measured at 2 years: pain or discomfort interfering with normal activities and the physical component summary score of the SF-36 health-related quality-of-life survey. The study was begun in five centers located in both community and academic environments. At 18 months, a sixth site was added, and at 28 months, after enrollment of 145 patients, one of the centers was terminated for reasons related to inadequate follow-up; all data from this center were deleted. As a routine measure, an independent, experienced, trial manager audited all clinical sites.

*Results:* Enrollment of patients began in January 2000 and will end on December 31, 2002. As of November 1, 2002, 637 patients had been randomized, 85% of the target enrollment. An additional 2,115 patients were screened but not randomized, yielding a recruitment rate of 23.1%. Analysis and publication of the results of the study will take place on completion of the minimum 2-year follow-up period for all patients.

*Conclusions:* A trial to compare the outcomes of watchful waiting and operation for management of inguinal hernias in men is needed to provide data to surgeons and to patients that can aid in choice of treatment. A description of the design of such a trial is presented.

*(J Am Coll Surg 196:737-742, 2003)*
*CSPCC Hines, IL*

# Tension-Free Inguinal Hernia Repair: The Design of a Trial to Compare Open and Laparoscopic Surgical Techniques

LEIGH NEUMAYER, MD, FACS, OLGA JONASSON, MD, FACS, ROBERT FITZGIBBONS JR, MD, FACS, WILLIAM HENDERSON, PHD, JAMES GIBBS, PHD, C JAMES CARRICO, MD, FACS, DAMAL ITANI, MD, FACS, LAWRENCE KIM, MD, FACS, THEODORE PAPPAS, MD, FACS, DOMENIC REDA, PHD, DOROTHY DUNLOP, PHD, MARTIN MCCARTHY, PHD, DENISE HYNES, RN, PHD, ANITA GIOBBIE-HURDER, MS, MARTIN J LONDON, MD, STEPHANIE HATTON-WARD, RN

**Abstract:** *Background:* Inguinal hernia is a common condition in men and represents a large component of health-care expenditures. Approximately 700,000 herniorrhaphies are performed each year in the United States. The most effective method of repair of an inguinal hernia is not known.

*Study Design:* A multicenter, randomized, clinical trial was designed to compare open tension-free inguinal hernia repair with laparoscopic tension-free repair on recurrence rates, complications, patient-centered outcomes, and cost. The study design called for randomization of 2,200 men over a period of 3 years. These men will be followed for a minimum of 2 years. This will allow determination of as little as a 3% absolute difference in recurrence rates with 80% power. Randomization is stratified by hospital, whether the hernia is unilateral or bilateral and whether the hernia is primary or recurrent.

*Results:* This is a report of the study design and current status. The study involves 14 Veterans Affairs medical centers with previous experience in laparoscopic hernia repair. After 35 months of enrollment, 2,164 men were randomized, and recruitment was then closed. The majority of the patients (82.3%) had unilateral hernias, and 90.6% of the hernias were primary. Sixty-seven percent of the patients had an outpatient operation.

*Conclusions:* We report successful recruitment into a large multicenter trial comparing open and laparoscopic hernia repair. When follow-up is complete, this study will provide data regarding both clinical (recurrence rates) and patient-centered outcomes.

*(J Am Coll Surg 196:743-752, 2003)*
*CSPCC Hines, IL*

# CSP #359

# A Clinical Trial Comparing the Safety and Efficacy of Alpha Blockade and Androgen Suppression for the Treatment of Benign Prostatic Hyperplasia (BPH)

Nocturia (awakening from sleep at night to void) is common in older adults, with over 60% of men older than 70 years experiencing two or more episodes nightly. Nocturia is also a well-recognized symptom of benign prostatic hyperplasia (BPH). The objective of this study was to evaluate the efficacy of medical therapy on nocturia in men with benign prostatic hyperplasia (BPH).

A secondary analysis of the CSP #359 trial database was undertaken, examining the effect of medical therapy (terazosin, finasteride, combination or placebo) on men who both completed 12 months of the trial and had at least one episode of nocturia at baseline (1,040 patients out of a total of 1,229 men randomized). Overall, nocturia decreased from a baseline mean of 2.5 episodes per night to 1.8, 2.1, 2.0 and 2.1 episodes in the terazosin, finasteride, combination and placebo groups, respectively. Of men with 2 or more episodes of nocturia per night at baseline (788 patients), a 50% reduction in nocturia was seen in 39%, 25%, 32% and 22% of the terazosin, finasteride, combination and placebo groups, respectively. In conclusion, Terazosin and combination therapy reduced nocturia in men with BPH, with the advantage of terazosin over placebo being a net reduction of 0.3 nocturia episode. Of those men with 2 or more episodes of nocturia at baseline, 39% of the terazosin group experienced a 50% or greater reduction in nocturia while only 22% of the placebo group achieved the same result. Changes in nocturia had a moderate impact on symptom-specific quality of life measures.

## Changes in Nocturia From Medical Treatment of Benign Prostatic Hyperplasia: Secondary Analysis of the Department of Veterans Affairs Cooperative Studies Trial

THEODORE M. JOHNSON, II, KAREN JONES, WILLIAM O. WILLIFORD, MICHAEL H. KUTNER, MUTA M. ISSA AND HERBERT LEPOR

**Abstract**: *Purpose*: We evaluate the efficacy of medical therapy on nocturia in men with benign prostatic hyperplasia (BPH).

*Materials and Methods:* We performed a secondary analysis of data from the VA Cooperative Study Program Trial in which 1,229 men with BPH 45 to 80 years old were randomly assigned to receive terazosin, finasteride, combination or placebo.

*Results*: The 1,078 men who completed 12 months of the trial are included in this study. Of those men 1,040 (96.5%) had at least 1 episode of nocturia at baseline, and 38 (3.5%) had less then 1 episode (baseline nocturia is an average of 2 measures). Of

those 1,040 men 788 (75.8%) had 2 or more nocturia episodes. Overall, nocturia decreased from a baseline mean of 2.5 to 1.8, 2.1, 2.0 and 2.1 episodes in the terazosin, finasteride, combination and placebo groups, respectively. Of men with 2 or more episodes of nocturia 50% reduction in nocturia was seen in 39%, 25%, 32% and 22% in the terazosin, finasteride, combination and placebo groups, respectively. Changes in nocturia were correlated with changes in reported bother from nocturia (Pearson correlation 0.48), BPH impact index (0.32) and overall satisfaction with urinary symptoms (0.33).

*Conclusions*: Terazosin and combination therapy reduced nocturia in men with BPH, yet the net advantage of terazosin over placebo was a net reduction of 0.3 nocturia episode. For a person to reach a 50% or greater reduction in nocturia, the advantage of terazosin over placebo was 17 percentage points. Changes in nocturia had a moderate impact on symptom specific quality of life measures.

*(J Urol 170:145-148, 2003)*
*CSPCC Perry Point, MD*

# CSP #256

# Vietnam Era Twin Registry

To determine the contribution of heredity to erectile dysfunction (ED), a classical twin study was conducted in the Vietnam Era Twin Registry. Information on two self-report measures of ED, difficulty in having an erection and difficulty in maintaining an erection, were gathered from 890 monozygotic and 619 dizygotic pairs. The estimated heritability of liability for dysfunction in having an erection is 35% and in maintaining an erection is 42%. Adjustment for established ED risk factors did not appreciably alter the estimated heritabilities. This study demonstrates an ED-specific genetic component that is independent of genetic influences on known ED risk factors.

## A Twin Study Of Erectile Dysfunction

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JACOBSEN SJ, GOLDBERG J

**Abstract:** *Background*: The extent of genetic influence on erectile dysfunction (ED) is unknown. This study determines the contribution of heredity to ED in a sample of middle-aged men.

*Methods*: A classical twin study was conducted in the Vietnam Era Twin Registry, a national sample of male-male pairs (mean birth year, 1949) who served on active duty during the Vietnam era (1965-1975). A 1999 male health survey was completed by 890 monozygotic (MZ) and 619 dizygotic (DZ) pairs. The prevalence and heritability of 2 self-report indicators of ED, difficulty in having an erection and in maintaining an erection, are estimated.

*Results*: The prevalence of difficulty in having an erection is 23.3% and in maintaining an erection is 26.7%. Twin correlations for dysfunction in having an erection are 0.35 (95% confidence interval [CI], 0.28-0.41) in MZ and 0.17 (95% CI, 0.09-0.27) in DZ pairs. For dysfunction in maintaining an erection, the twin correlations in MZ and DZ pairs are 0.39 (95% CI, 0.32-0.45) and 0.18 (95% CI, 0.09-0.27), respectively. The estimated heritability of liability for dysfunction in having an erection is 35% and in maintaining an erection is 42%. The heritable influence on ED remained significant after adjustment for ED risk factors.

*Conclusion*: The present study demonstrates an ED-specific genetic component that is independent of genetic influences from numerous ED risk factors. The results suggest that future molecular genetic studies to identify ED-related polymorphisms are warranted.

*(Arch Intern Med 164:165-168, 2004)*
*ERIC Seattle, WA and CSPCC Hines, IL*

# The Vietnam Era Twin Registry

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The Vietnam Era Twin (VET) Registry is composed of 7369 middle-aged male-male twin pairs both of whom served in the military during the time of the Vietnam conflict (1965-1975). The Registry is a United States Department of Veterans Affairs resource that was originally constructed from military records; the Registry has been in existence for more than 15 years. It is one of the largest national twin registries in the US and currently has subjects living in all 50 states. Initially formed to address questions about the long-term health effects of service in Vietnam the Registry has evolved into a resource for genetic epidemiologic studies of mental and physical health conditions. The management and administration of the VET Registry is described with particular attention given to the processes involved with database maintenance and study coordination. Several waves of mail and telephone surveys have collected a wealth of health-related information on Registry twins. More recent data collection efforts have focused on specific sets of twin pairs and conducted detailed clinical or laboratory testing. New Registry initiatives for the future include the construction of a web site and the development of a DNA repository.

*Results:* The twin identification process from military records took approximately 3 years from 1983-1986. Since that time there have been four research initiatives that have attempted to collect information from all twins on the VET Registry. We present a snapshot of data available from the: a) 1983-1986 Registry military record, b) 1987 Survey of Health, c) 1991 National Heart Lung and Blood Institute Survey, d) 1993 Harvard Twin Study of Substance Abuse, and e) 1999 Male Health Survey.

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# Comparison of Anterior and Posterior Chamber Lenses Implants After Vitreous Loss in Attempted Extracapsular Cataract Extraction

When a person has a cataract removed surgically, a plastic (intraocular) lens is put into the eye to replace the natural lens that was removed. The replacement lens can be one of two types; the 'anterior' intraocular lens (IOL) that is placed in front of the iris and the 'posterior' IOL that is placed behind the iris. During cataract surgery, there is sometimes a complication, called 'vitreous presentation' which can lead to later problems with vision.

The VA Cooperative Cataract Study was designed to find out whether it was better to use an anterior or posterior IOL when vitreous presentation occurred during cataract surgery. Patients with this complication were randomized to receive one or the other of the IOL's. Their vision was measured one year after surgery. It was found that more patients who received the posterior lens had good vision at one year than those who received the anterior lens. There were about the same number of eye problems following surgery in the two groups. Therefore, the study recommended that patients who suffer vitreous presentation during cataract surgery should have a posterior lens inserted into the eye.

## A Comparison of Anterior Chamber and Posterior Chamber Intraocular Lenses After Vitreous Presentation During Cataract Surgery: The Department of Veterans Affairs Cooperative Cataract Study

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**Abstract:** *Purpose:* To compare the efficacy and safety of anterior chamber (AC) intraocular lenses (IOLs) and posterior chamber (PC) IOLs implanted after vitreous presentation during extracapsular cataract extraction (ECCE).

*Design*: The study was a prospective, long-term, randomized clinical trial conducted at 19 Department of Veterans Affairs medical centers across the United States.

*Methods*: There were 438 eyes (438 patients) that met preliminary eligibility criteria, suffered vitreous presentation during ECCE (phacoemulsification or classical extracapsular technique), and had sufficient capsular support for a PC IOL without sutures after anterior vitrectomy randomized to either a PC IOL (230 patients) or an AC IOL (208 patients). Patients were examined at 3, 6, and 12 months postsurgery and yearly thereafter. Minimum follow-up was 1 year. The primary outcome measure of best-corrected visual acuity at 1 year was obtained by a masked certified examiner.

*Results*: More PC IOL patients (91%) achieved visual acuity of 20/40 or better at 1 year than AC IOL patients (79%), a highly significant difference (P= .003). There was no significant difference between the two groups for patient's rating of vision or adverse events. Over 84% of the PC IOL patients and over 77% of the AC IOL patients rated their vision as good or better at 1 year as opposed to only 7% giving such ratings before surgery. For at least one rating period during the first year, 13.2% of the combined study patients had cystoid macular edema, 8.5% had posterior capsule opacification, 5.7 had glaucoma, and 3.7% had retinal detachment.

*Conclusion*: In the presence of sufficient capsular support, a PC IOL should be implanted after vitreous presentation during ECCE.

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